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Pediatrics

VOLUME 12 SEPTEMBER 1953 NUMBER 3, PART I

ORIGINAL ARTICLES

CORTICOSTEROIDS AND ANTIDIURETIC SUBSTANCE IN NEPHROTIC CHILDREN

By ENRIQUE GALÁN, M.D., MANUEL PÉREZ-STABLE, M.D., ORLANDO GARCÍA FAEZ, M.D., EMILIO UNANUE, M.D., OTTO GARCÍA, M.D., JUAN M. LABOURDETTE, M.D., AND GILBERTO ALFONSO, M.D.

(with the technical assistance of Pedro Valledor)

Havana

INCREASE in urinary volume and disappearance of edema following administration of adrenocorticotrophic hormone (ACTH) and cortisone to patients suffering from the nephrotic syndrome have been reported by several investigators.[1-6] This therapeutic approach to edema does not rule out the primary renal nature of the nephrotic syndrome. In spite of the remarkable diuretic effect of such compounds it was found that the disease follows its usual course in most cases and temporary improvement of renal function does not go beyond the limit allowed by the remaining normal nephrons.

Changes in tubular reabsorptive capacity were found in some of the authors' cases[7, 8] during studies on clearance tests and albumin therapy. The authors suggested that nephrotic edema was partly dependent upon increased tubular reabsorption. This was also the opinion of Eder and collaborators[9] and it was so commented upon by H. W. Smith,[10] in a critical analysis. An increase in urine output, on the other hand, may occur not only after an increase in the glomerular filtration rate (GRF) above previous value[3, 11-13] but also from a decreased tubular reabsorption[8, 14] and with or without changes in the filtration fraction.[15] The endocrine role in nephrotic edema and in spontaneous and induced diuresis has been studied by only a few individuals. Robinson and Farr[16] reported the

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presence of an antidiuretic (ADH-like) substance in the urine of edematous patients. Deming and Luetscher[17] found, by a biologic assay, increased excretion of a sodium-retaining desoxycorticosterone-like material in nephrotic patients. More recently, Farnsworth and Dupee[18] were of the opinion that corticoids determined by periodic acid were difficult to interpret. Values 10 times higher were observed on using glucoronidase in the determination of steroids. From these considerations it seemed justified to investigate simultaneously the presence of corticosteroids in urine and of the antidiuretic substance in the blood of nephrotic children. Since urinary excretion of steroids may not be a reliable index of adrenal function in cases with diseased kidneys, determinations were also carried out on blood and ascitic fluid.

Methods of Study

Determination of Corticosteroids: The chromotropic-sulfuric reaction for formaldehyde[19] was used as previously reported.[20–22] An aliquot of urine was hydrolyzed by addition of concentrated HCl to a pH of 1.0. Extraction of steroids was carried on with ethyl-acetate as recommended by Tobian.[21]* Resulting extract was treated 3 times with 25 cc. portions of 2N NaOH for removal of urinary pigments and was then washed 3 times with 50 cc. portions of distilled H_2O and dehydrated with anhydrous Na_2SO_4. It was evaporated to dryness at 45°C. in vacuo. Dried extract was suspended with glacial acetic acid 0.5 cc. and distilled H_2O 8.5 cc. Oxidation was done for 45 min. with 0.03 M KIO_4 4 cc. in 0.036 MH_2SO_4. At the end of this period $SnCl_2$ 0.5 cc. was added to stop oxidation. After centrifugation, excess of $SnCl_2$ in decanted fluid was precipitated by addition of 2% solution of ammonium hydroxide 2.0 cc.† It was again centrifuged and finally filtered through a 3 Whatman filter paper. Distilled H_2O 6.0 cc. and 5M H_2SO_4 3.0 cc. were added to 6.0 cc. of filtrate. Five cubic centimeters of a 7% freshly-prepared chromotropic-sulfuric reagent were added to 3.0 of diluted extract and it was heated in a vigorously boiling water bath for 30 min. It was cooled at room temperature and 9M H_2SO_4 cc. were added. Two blanks were run simultaneously. One was treated the same way as dried extract, the other by adding distilled H_2O 3.0 cc. to the chromotropic-sulfuric reagent. Iodine present was removed by filtration of colored fluid through a #42 Whatman paper.† Color was read in a Coleman Jr. spectrophotometer at 570 μμ. Tests were always made in duplicate.

Calibration was performed with formaldehyde, hexamethylenetetramine and DOCA.‡ Curves are shown in chart 1. Values are expressed in terms of mg. 11-desoxycorticosterone/day in urine, in mg./100 cc. in plasma and per cent total volume of ascitic fluid removed. Plasma and ascitic fluid

---

* The low specific gravity of ethyl-acetate prevents formation of emulsions in the presence of albuminuria more effectively than does chloroform, thus minimizing losses of extractable material. When an emulsion was formed in the presence of heavy albuminuria it was usually broken by addition of 3 portions of 25 cc. of 2N NaOH and 50 cc. ethanol. Test was then repeated after previous precipitation of protein with trichloroacetic acid. Precipitated protein was resuspended to same original volume with saline solution and extracted in a similar manner. The amount of steroid found in such protein fraction averaged 0.0075 mg./100 cc. suspension. Extraction steps were carefully checked for amounts of ethyl-acetate lost.

† The chromotropic-sulfuric reaction with formaldehyde obtained by KIO_4 oxidation showed interference of color formation from the presence of $SnCl_2$ and free iodine. The first one was removed by centrifugation at 3,000 rpm and treatment of supernatant fluid with a 2% ammonium hydroxide solution 2 cc. followed by a second centrifugation and filtration through a #42 Whatman filter paper. Free iodine present in colored fluid was removed by filtration through same filter paper and adsorption by the starchy material present in it. These 2 additional steps to the technic reported by Tobian[21] made distillation unnecessary and have given reliable results in the authors' hands. Colorimetric readings were made by setting the water-chromotropic-sulfuric blank to zero optical density and subtracting from analyzed samples the optical density of the periodate-chromotropic-sulfuric blank.

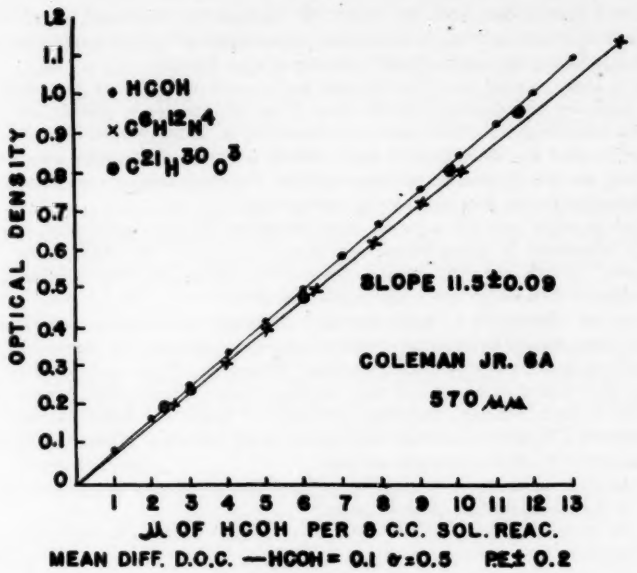

CHART 1.

· HCOH = Formaldehyde
× C6H12N4 = Hexamethylenetetramine
⊙ C21H30 03 = 11-desoxycorticosterone

steroids were determined by same procedure except for hydrolysis with HCl. Recovery assay was done by adding known amounts of DOCA to urine specimens.‡

Antidiuretic (ADH-like) substance in blood serum: Determination of antidiuretic activity of nephrotic sera was studied by the method of Birnie and collaborators[23, 24] as used by Lloyd and Lobotsky.[25] Male Sprague-Dawley rats weighing around 200 gm. each were kept in individual cages fitted to make an accurate collection of urine and maintained under same condition of temperature and humidity. They were hydrated for 18 hr. previous to onset of test. Two animals were taken as controls and received intraperitoneal injection of saline solution; 2 had nephrotic serum and 1 had pitressin 5 milliunits (mu). They received the same amount of water/100 sq. cm. body surface. Urinary output was measured at ½ hr. intervals after injection of assay material.

Calculation:

$W1 = T_{H_2O}\ U_h$ (1)

$\%\ DR = V_e/W1 \times 100$ (2)

ADS units = % DR control − % DR experiment (3)

Where: W1 water load. T_{H_2O} total water intake. U_h = total diuresis during hydration period. V_e = total diuresis at 90 min. test. DR = diuretic response.

ADS activity of 1.0 cc. normal serum was estimated around 5 mu. pitressin. Presence of antidiuretic activity is expressed at plus rat units/cc. serum. A mean value of −7 rat units (S.E. ± 0.9)

‡ Desoxycorticosterone acetate (DOCA) was found suitable for calibration after addition of 2% NaOH solution up to a pH of 10 to aliquots of DOCA stock solution in methanol. Urine specimens for recovery-assay were previously hydrolyzed and extracted and then treated with NaOH in a similar manner, up to a pH of 10. A mean value of 99.5% recovery with a standard error of ±1.6 was calculated from a total of 15 recovery assays. An equivalent amount of DOCA as shown in calibration curve was calculated by subtracting molecular weight of acetic acid from DOCA (DOC/DOCA:0.84).

was found in 6 control determinations. Under the conditions of those experiments a +1 rat unit was considered equivalent to 1 mu. pitressin. Rats were considered to have a sensitivity of 2mU/100 gm. body weight when given intraperitoneal injections of assay material.

In order to avoid personal bias determinations were carried on by one of the authors (E. U.) in a different laboratory and ignoring physical status of patient, changes in diuresis and steroid excretion. Animals were discarded after 6 tests in prevention of an antigen-antibody reaction. Sodium and Cl excretion in urine was determined in some animals and eosinophile counts were done after 3rd test to rule out any allergic reaction to foreign protein. Discarded animals were killed and examined for any pathology of kidney, liver and cardiovascular system.

Electrolytes in urine and blood serum were determined by photocolorimetry except for CO_2. Sodium was determined by precipitation with uranyl-zinc-acetate,[26] by cobalti-nitrate reaction,[27] Cl by silver iodate[28] and Ca and P by amino-2 naphthol-4 sulfonic acid.[29] Plasma proteins were determined by method of Greenberg[30] and by that of Wolfson et al.[31]

Blood urea was determined by Karr's method;[32] cholesterol was extracted with Bloor's alcohol-ether mixture and subjected to Lieberman-Burchard reaction.[33] Sedimentation rate was done by Westergren's method and hematocrit by Wintrobe's technic.[33] Phloxin stain[34] was used for eosinophile counts.

Clearance tests: Inulin (Cin), sodium-para-amino-hippurate clearance (Cpah) were done by original procedure of Smith, Shannon, Goldring and Chasis.[35, 36] Inulin was determined by the resorcinol-thiourea method.[37] Clearance of sodium thiosulphate (Cth) was done by titration technic.[38] Simultaneous clearances of Na, K were occasionally done.

Urinary sediment was examined by Addis count[39] and daily proteinuria was calculated by precipitating method on the Shevky-Stafford albuminometer.[39]

Plan of Study

Four children with clinical features of the nephrotic syndrome were studied. Two of them had no symptoms of glomerular involvement and two showed hematuria and azotemia. All cases, however, had a marked reduction in renal function as detected by clearance tests. One additional case of acute hemorrhagic nephritis was included in order to find out any differences in behavior of steroid excretion from those cases having the nephrotic syndrome. This case was studied through a period of spontaneous increase of diuresis. Three control cases were followed in a similar manner. Two of them were convalescents from Sydenham's chorea for two months prior to their study and one had a

TABLE 1

Periods of Study

Decrease of diuresis	1. Edema and oliguria*
	2. Intercurrent bacterial infection
	3. Empyema followed by shock and heart failure
	4. Oral intake of salt
	5. Therapy with ACTH not followed by diuretic response
Increase of diuresis	6. Spontaneous elimination of edema with increase in urinary output
	7. Therapy with CHPA followed by increase in urinary volume and elimination of edema
	8. Therapy with ACTH followed by increase in urinary volume and elimination of edema
	9. Spontaneous increase in urinary output in case of acute hemorrhagic nephritis
	10. Control cases

* The term "oliguria" is used to express a decrease in daily urinary volume below that found in control cases and the volume of urine observed in nephrotic children during the edematous phase of illness. "Diuresis" is used to express the daily urinary volume. By increase of diuresis is meant a urinary volume higher than that observed during the oliguric, edematous period and leading to total or partial elimination of edema, though in most cases it was lower than that of control cases. Spontaneous, induced diuresis and diuretic response are given the same meaning.

viral respiratory infection two weeks before. All three had a normal urinary sediment, renal function, blood chemical values and sedimentation rate. Clinical records included daily observation of the physical status of the patient (amount of edema, change in weight, diuresis, blood pressure), diet, liquid intake, medication and evidences of bacterial infection. All nephrotic children and the patient with acute hemorrhagic nephritis were offered the same basal diet. It was calculated to have protein 54 gm., salt 0.84 gm., water 1,800 cc. and around 1,000 to 1,250 calories/day. Electrolyte intake was similar in all cases as they were given the same type of food—lonolac ® milk and canned vegetables. The quantity of food taken was carefully measured daily and the diet was not changed, even in those periods of study where oral intake of salt and intravenous injection of low sodium concentrated human plasma albumin (CHPA) were given to one nephrotic child.

Urinary volume, proteinuria, excretion of electrolytes and steroids were determined daily. Blood chemical constituents and antidiuretic substance were simultaneously studied twice weekly. Clearance tests and urinary sediment were studied every two weeks.

Since the patients experienced several uncontrollable events, such as spontaneous elimination of edema and intercurrent bacterial infection, periods of observation were grouped as shown in table 1.

Results

Urinary Excretion of Corticosteroids: Values for normal infants and children have been reported by several investigators.[40-44] A wide fluctuation was observed according to the method involved in their determination.[20, 22, 40, 45-50] However, they approach normal adult value when determined by one of the known chemical procedures and corrected for sq. m. surface area.[44]

The control cases showed a higher value than that reported by King and Mason[50] in children of the same age. This discrepancy was probably due to differences in technic. On using the method described above a mean value of 1.42 mg./day/M.^{2} with a standard error of ±0.23 was calculated from a total of 25 determinations made in three control children 9 to 10 years of age (table 2). A total of 175 determinations were done in the

TABLE 2

Urinary Excretion of Formaldehydogenic Steroids in Nephrotic Children

Period of Study	No. of Observation	HCOH-Steroids mg./day/M^2 Mean	sdm	0	r	Urinary volume cc./day/M^2 Mean
1	49	1.25	0			489
2	17	4.75	x			587
3	9	0.76	x			302
4	7	1.17	0			351
5	26	1.85	x	±1.32	+0.380	673
6	20	1.16	0			900
7	20	0.73	x			643
8	24	4.00	x			906
9	3	3.57	x			769
10	25	1.42	—	±0.79	−0.320	1,490

0=standard deviation. sdm=significant difference between mean value of control cases[10] and mean values for other periods of study. r=coefficient of correlation between urinary excretion of steroids and urinary volume.

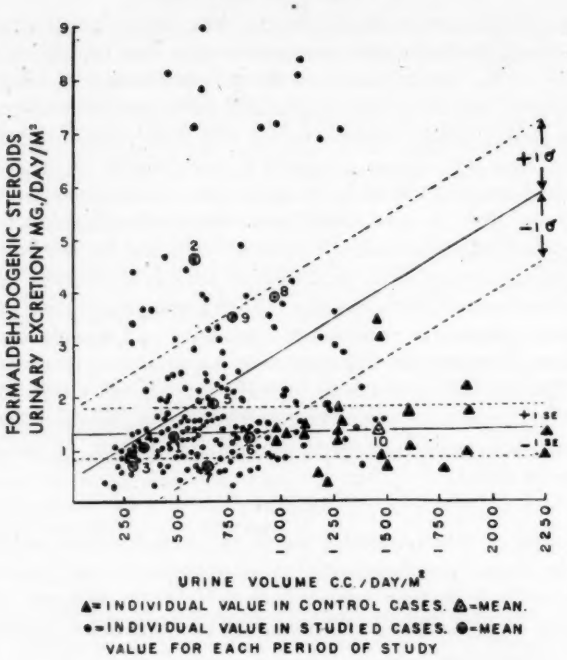

CHART 2.

cases studied; these are shown in chart 2 and 68% in chart 3. Excretion above the normal mean was seen in a total of 67 determinations, 50 of them during ACTH therapy and for a variable time after the withdrawal of hormone (periods 5 and 8), and 17 occurred in the course of bacterial infection (period 2). A high steroid output was also observed in the case of acute hemorrhagic nephritis during spontaneous elimination of edema (period 9).

Values below the normal mean were seen in a total of 56 determinations made during periods of shock (3), oral intake of salt (4) and during spontaneous elimination of edema (6) and that induced by CHPA (7). There was no statistical difference between the mean control value and that found in 49 determinations during periods of oliguria and edema.[1] The lowest values were observed during shock (period 3) and CHPA therapy (period 7). A significant difference was observed between ACTH-treated cases showing diuretic response (period 8) and those having no elimination of edema and no increase in urine volume (period 5). In two instances of ACTH diuresis there was a total steroid excretion of 153 mg./M² in 22 days, while in two having no diuretic response there was only a total excretion of 73.4 mg./M² during same number of days.

Nephrotic children showed a low excretion of steroids during spontaneous increase in urinary volume and elimination of edema, while the one with hemorrhagic nephritis showed a rise of urinary steroids during the same clinical event. A similar difference was observed between steroid excretion during ACTH and CHPA therapy, the last one showing a marked decrease in output with simultaneous rise in urinary volume.

The scatter diagram in chart 2 shows a correlation of urinary steroids with urinary volume in nephrotic children. Such a correlation was not found in control cases.

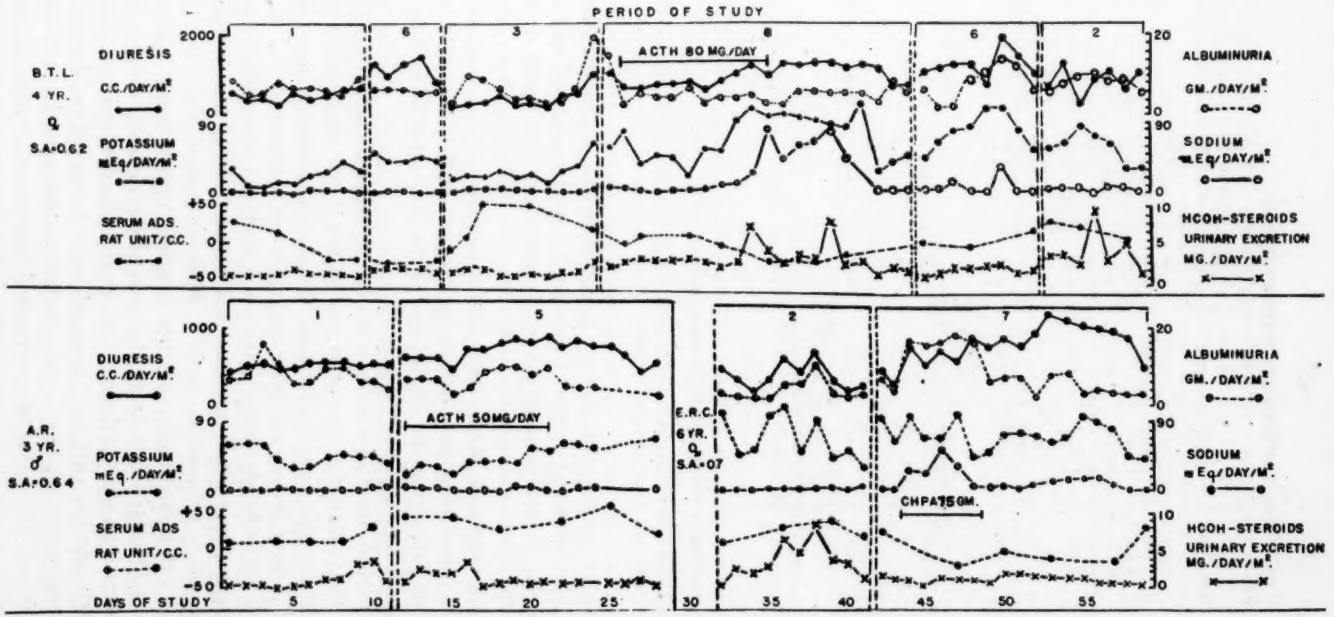

CHART 3. Sequence of events through periods 1, 2, 3, 5, 6, 7 and 8 of study in 3 nephrotic children. Chart shows 50% of observations on ADS and 68% on H_2O, protein, Na, K and steroid excretion in urine. Note changes in ADS preceding or coincident with changes in water excretion. Increase in steroid output during therapy with ACTH (periods 5 and 8) and bacterial infection (period 2). Increase in sodium excretion occurred only during diuretic response to ACTH and CHPA (periods 7 and 8). Excretion of K increased with increase in H_2O and steroid output. Proteinuria averaged 6.80 gm./day/M^2 for all periods except period 7. This period showed average of 14.9 gm./day/M^2 of proteinuria during 5 days of CHPA therapy.

TABLE 3

CLEARANCE OF FORMALDEHYDOGENIC STEROIDS

Case, Age, Sex, sa.	P mg./100 cc.	U mg./100 cc.	V cc./day/M²	UV/100 mg./day/M²	U/P ratio	UV/P cc./day/M²	*C_{in} or ♯C_{th} cc./mte./M²	Period of Study
B.T.L. 4 yr., F 0.62	0.25	0.164	395	0.65	0.66	2.53	♯35.2	1
	0.10	0.116	806	0.93	1.16	9.38	♯58.9	6
	0.24	0.156	1,367	2.13	0.65	9.02	♯51.5	8
	1.25	0.776	1,043	8.09	0.62	6.48	*27.8	8
J.V. 11 yr., M 1.02	1.40	0.396	225	0.89	0.28	0.63	*25.4	1
A.R. 3 yr., M 0.64	0.23	0.169	859	1.45	0.73	6.24	—	8
M.A.F. 12 yr., F 1.58	0.40	0.629	525	3.24	1.57	8.20	*15.0	9
M.R.G. 10 yr., F 1.15	0.40	0.237	826	1.95	0.59	3.54	*38.0	10
P.L. 10 yr., M 1.23	0.30	0.100	699	0.69	0.33	2.34	*72.2	10

sa = surface area. P = plasma steroids. U = urinary steroids. V = urinary volume.

$\frac{UV}{100}$ = urinary excretion of steroids. $\frac{UV}{P}$ = clearance of steroids. C_{in} and C_{th} = clearance of inulin and thiosulfate, respectively, (glomerular filtration rate).

2. Renal Clearance of Steroids: The date are presented in table 3. No simultaneous determinations of GFR (inulin and thiosulfate clearances) and plasma steroids were done due to the large amount of blood required for analytic procedures. The steroid clearance was compared with the nearest determination of filtration rate. The results were corrected for surface area and are expressed in cc. plasma cleared/day/m².

Clearance study of formaldehydogenic steroids has not been reported for normal children so the results are compared to the values found in the two control subjects and the patient with acute hemorrhagic nephritis.

A significant correlation was found between steroid clearance and urinary output in nephrotic children. The coefficient of correlation was +0.882. It was not so significant in the control cases, the clearance being higher than that of control cases through periods of spontaneous and induced diuresis and lower during periods of oliguria.

Plotting the steroid excretion against the V/Cin and V/Cth ratio, as is done in chart 4, shows a definite relationship for both nephrotic and control children. The V/Cin and V/Cth ratio relates urinary volume/min. to GFR. With no changes in Cin or Cth, V value increases along with a simultaneous reduction in tubular reabsorption of water.

The U/P ratio of a filterable solute should also decrease approaching a theoretic value of 1.0 at the time there is no active reabsorption of water in the distal segment. According to Smith[10] a U/P ratio from 8:3 was found for inulin during osmotic diuresis and after inhibition of antidiuretic hormone in experimental diabetes insipidus. The steroid U/P ratios were 1.16 and 1.57 in the two instances of spontaneous increase in urinary volume which occurred in a nephrotic child (Case B.T.L. and the patient with acute

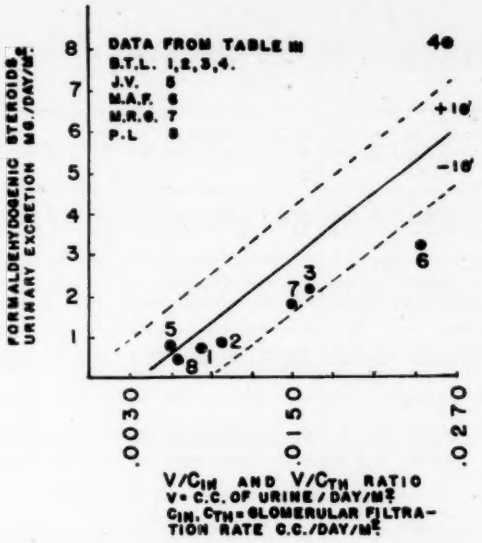

CHART 4.

hemorrhagic nephritis). The last one showed also a U/P ratio of 8.3 for inulin and 6.0 for K and yet inulin clearance was only 26 cc./mte./M². In 4 out of 5 instances of increase in urinary volume with elimination of edema and increase in steroid clearance shown in table 3 the GFR was always below the normal value for children. Though no definite conclusion can be drawn from such a few observations steroid excretion seems to increase proportionally to the increase in V/Cin and V/Cth ratio in all cases, suggesting the participation of tubular reabsorption in the urinary excretion of steroids in nephrotic children.

Corticosteroids in plasma: Plasma steroids in normal children have not as yet been reported. The authors' two control cases averaged 0.36 mg./100 cc. plasma which corresponded to the value reported by Corcoran and Page[22] in normal adults. Results are shown in table 4 together with simultaneous determinations of plasma constituents and eosinophile counts.

Case B.T.L. had 0.25 mg./100 cc. plasma during period 1. It decreased to 0.10 mg. at the end of a spontaneous increase of diuresis and disappearance of edema. No plasma steroids were found while she was suffering from shock (period 3). It increased from 0.24 to 1.25 mg./100 cc. in the course of ACTH therapy. A value of 2.12 mg./100 cc. was found during an intercurrent bacterial infection. This patient did not have a diuretic response to a second course of ACTH so a few days later an intravenous drip of ACTH 20 mg. added to 5% dextrose 300 cc. was started. At the beginning of the infusion she had a marked urticarial reaction, diffuse erythema, tachycardia and her eosinophile count rose from 200 to 1093/cmm. Her plasma steroids were 0.27 mg./100 cc. 24 hours after the allergic reaction and there was no diuretic response. Patient A.R. had 0.23 mg./100 cc. at the end of ACTH treatment which was not followed by increase in diuresis. He died from uremia in the second year of illness. A concentration of 1.4 mg./100 cc. plasma was found in Patient J.V. during a period of oliguria and edema (period 1).

TABLE 4

CHANGES IN PLASMA CHEMICAL CONSTITUENTS, EOSINOPHILE COUNTS AND SEDIMENTATION RATE WITH SIMULTANEOUS OBSERVATIONS ON ADS AND URINARY AND PLASMA STEROIDS IN NEPHROTIC CHILDREN

Case, Age, Sex, Period of study	ADS Rat unit/cc. serum	Corticosteroids		Eosinophile/cmm.	Cholesterol mg./100 cc.	Plasma Proteins gm./100 cc.			Electrolytes mEq./l.				Sedimentation rate mm./hr.
		Urine mg./day/M2	Plasma mg./100 cc.			Total	Albumin	Globulins	Na	K	Cl	CO^2	
B.T.L. 4 yr., F													
1	+27	0.84	—	131	440	4.00	2.50	1.90	134	4.5	102	11.3	144
	+12	0.90	0.25	150	460	5.33	1.79	3.54	135	4.9	98	18.5	142
2	+15	2.95	—	106	440	5.33	—	—	142	5.0	112	16.0	140
	+14	5.46	—	100	440	4.00	1.16	2.84	142	4.6	100	17.0	155
	—	3.57	—	137	572	3.20	1.35	1.85	151	3.7	118	—	160
	—	—	2.12	150	400	3.05	0.14§	2.91	151	5.6	117	13.0	155
3	+48	0.42	0	68	480	6.09	2.98	3.10	130	6.4	98	15.3	144
5	+15	3.94	—	40	500	3.50	0.23§	3.35	151	5.1	132	17.0	163
6	−25	0.93	0.10	150	750	5.21	1.92	3.29	135	4.6	108	18.0	144
	−10	1.60	—	130	—	3.85	—	—	132	—	112	—	160
	—	1.17	—	108	364	4.57	1.85	2.72	142	5.2	—	19.0	165
8	− 6	2.08	—	25	520	5.56	2.25	3.31	125	4.2	96	21.0	142
	− 5	3.76	0.24	74	440	6.09	3.16	2.93	145	4.2	92	25.0	80
	−25	3.10	—	192	334	6.10	3.10	3.00	145	4.4	110	20.0	75
	—	7.12	—	6	525	3.40	0.30§	3.10	137	5.2	124	16.0	160
	—	2.46	1.25	13	525	3.20	0.33§	2.87	132	5.0	118	—	—
	—	1.27	—	38	450	3.60	0.28‡	1.52	142	5.6	—	23.0	155
A*	—	5.03	0.27	1,093	400	2.82	0.15§	2.67	151	6.7	119	1.70	—
E.R.C. 6 yr., F													
1	+ 1	3.66	—	120	334	4.60	3.40	1.20	135	5.2	104	15	—
	+12	1.12	—	180	375	3.87	1.58	2.29	145	5.2	100	24	—
	+16	0.85	—	160	385	5.33	1.81	3.52	147	5.4	116	21	—
2	+21	7.74	—	15	400	4.60	3.20	1.40	135	5.9	104	23	—
4	+20	0.28	—	80	730	4.00	2.60	1.40	135	5.9	104	34	—
	+30	1.91		60	500	3.55	1.80	1.75	148	5.9	108	23	—
6	− 2	0.57	—	170	370	5.33	1.96	3.37	143	5.2	106	23	—
	−15	0.90	—	180	345	4.74	1.73	3.01	148	6.3	109	21	—
	−23	0.72	—	—	—	5.56	1.99	3.57	145	—	114	18	—
B†	+ 8	0.81		40	364	3.55	1.80	1.75	140	5.6	106	33	—

TABLE 4—(*continued*)

	−23	0.72	—	—	—	3.56	1.99	3.81	140		111		
B†	+ 8	0.81		40	364	3.55	1.80	1.75	140	5.6	106	33	—

TABLE 4—(*continued*)

Case, Age, Sex, Period of study	ADS Rat unit/cc. serum	Corticosteroids		Eosinophile/cmm.	Cholesterol mg./100 cc.	Plasma Proteins gm./100 cc.			Electrolytes mEq./l.				Sedimentation rate mm./hr.
		Urine mg./day/M2	Plasma mg./100 cc.			Total	Albumin	Globulins	Na	K	Cl	CO^2	
A.R. 3 yr., M 1	+ 4	0.87	—	500	296	3.63	1.04	2.59	144	—	111	17	—
	− 6	1.51	—	300	462	3.97	1.35	2.62	—	5.0	103	18	—
	+ 5	1.51	—	150	436	4.05	1.08	2.97	152	8.0	85	19	—
5	+12	1.70	0.23	25	424	3.84	1.58	2.26	146	6.5	62	18	—
	+ 5	1.32	—	150	436	4.13	1.41	2.72	140	10.0	45	20	—
	+12	1.56	—	0	349	4.98	1.75	3.23	147	8.5	42	20	—
	+11	1.40	—	250	296	3.63	1.04	2.80	112	9.6	78	19	—
J.V. 11 yr., M 1	+ 6	1.40	1.40	160	—	6.00	1.68	4.37	137	4.5	92	—	—
6	—	0.35	—	150	—	2.75	0.20§	2.55	132	6.2	99	20	—
	—	0.98	—	100	—	2.45	0.29§	2.16	147	6.2	—	—	—
C‡	+14	2.37	—	30	400	3.15	0.81§	2.34	147	6.2	112	—	—
	—	2.80	—	25	290	2.70	0.22§	2.48	147	6.8	115	19	—
M.A.F. 12 yr., F 9	—	3.81	0.40	200	190	5.05§	1.08§	3.97	151	5.6	132	—	50
		3.17	—	250	180	—	—	—	151	4.1	138	—	—
P.M.C. 9 yr., F 10	−10	0.75	—	500	160	6.40	4.10	2.30	145	4.5	72	23	6
M.R.G. 10 yr., F 10	− 8	0.58	0.40	210	—	—	—	—	—	—	—	—	—
	+ 5	0.75	—	350	160	6.50	4.50	2.00	153	4.9	102	—	—
P.L. 10 yr., M 10	−10	0.69	0.30	250	190	—	—	—	—	—	—	—	—
	− 8	1.01	—	270	—	—	—	—	—	—	—	—	—

A* Allergic reaction to i.v. ACTH.
B† After ACTH 25 mg.
C‡ After ACTH 25 mg.
§ Serum proteins determined by technic of Wolfson et al.

TABLE 5

FORMALDEHYDOGENIC STEROIDS IN ASCITIC FLUID OF NEPHROTIC CHILDREN

Case Sex Age	Date	HCOH-Steroids mg./100 cc.	HCOH-Steroids Total mg. in ascitic fluid	Ascitic fluid removed Total cc.	Period of Study
B.T.L. F, 4 yr.	X-11 1950	0.26	—	*	1
	II-24 1951	1.80	31.00	1,725	6†
	IV-21 1951	0.66	20.90	3,161	8
	V-8 1951	0.38	7.90	2,077	1‡
J.V. M, 11 yr.	IV-4 1951	0.13	6.96	5,330	1
A.R. M, 3 yr.	X-23 1950	0.32	—	*	5
E.R.C. F, 6 yr.	VIII-15 1950	0.31	—	*	1
	X-7 1950	0.51	10.00	2,000	1

* 150 cc. removed only for determination of steroids.
† At termination of para-amino-hippuric-inulin infusion.
‡ Four days after allergic reaction to i.v. ACTH.

Corticosteroids in Ascitic Fluid: Diffusibility of adrenal steroids across the peritoneal membrane was demonstrated by the presence of formaldehydogenic material in specimens of ascitic fluid from nephrotic children. These findings are shown in table 5. The total steroid content was calculated from the total volume of ascitic fluid removed. Unless substances other than adrenal steroids give the formaldehyde reaction it seems probable that a large quantity of such compounds can be retained in the increased volume of extracellular fluid in nephrotic children during the oliguric and edematous phase. Values from 6.96 to 31 mg. formaldehydogenic substance were found in the authors' cases. Simultaneous plasma and ascitic fluid determinations gave a plasma steroid/ascitic fluid steroid-concentration ratio of 10 in Patient J.V. during period 1, and 1.89 in Patient B.T.L. during ACTH therapy (period 8). However, most determinations in ascitic fluid showed values close to those in plasma. Hetcher[45] has stated that none of the noncorticoid formaldehydogenic material passes a dialyzing membrane, so it seems probable that the material found in ascitic fluid is mostly adrenal steroids, though it remains to be demonstrated whether it is an active material. The authors are carrying on chromatographic studies on this problem which will be reported at a later date. It should be noted that the intraperitoneal injection of ascitic fluid into rats did not cause any oliguric effect.

TABLE 6

ANTIDIURETIC SUBSTANCE IN BLOOD SERUM OF NEPHROTIC CHILDREN

Period of Study	No. of Observation	ADS Rat unit/cc. of serum Mean		Urine Volume cc./day/M² Mean
1	22	+16		543
2	11	+20		396
3	6	+21		494
5	15	+17	r−0.713	544
6	12	−16		966
7	4	−11		778
8	7	− 4		1,000
10	6	− 7		2,780

ADS = Antidiuretic substance. r = coefficient of correlation between antidiuretic substance and urine volume.

Antidiuretic (ADH-like) Substance in Blood Serum: Results are shown in chart 5 and table 6. Control cases having an average diuresis of 2,780 cc./day/M² showed a mean value of −7 rat unit/cc. blood serum with a range of −5 to −11 and a standard error of ±0.9.

Antidiuretic substance (ADS) was not studied during periods 4 and 9. A significant correlation between antidiuretic activity and urinary output was found for all periods of study (r = −0.713). Eighty-three per cent of the determinations fell within +2 standard

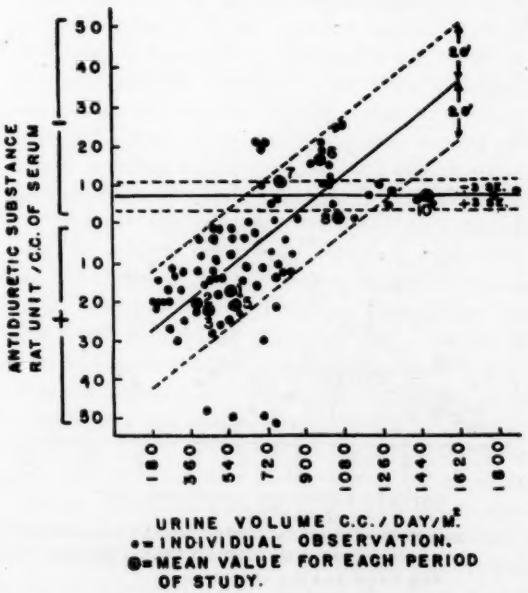

CHART 5.

deviation of the regression line calculated from all periods of observation. A significant difference between the mean control value (period 10) and mean values for periods 1, 2, 5 and 6 was also found. Antidiuretic activity of blood serum showed a better correspondence with changes in diuresis than formaldehydogenic steroids. Rapid variation in antidiuretic activity was also seen to correspond with more or less sudden changes in diuresis. For instance, Case B.T.L. who had symptoms of shock and heart failure experienced a quick rise of antidiuretic activity of her blood serum from −20 in the absence of edema with a urinary output averaging 925 cc./day/M², to +45 rat unit on the third day of shock when the urinary output had decreased to 125 cc./day/M². Four days afterwards the antidiuretic activity decreased to +13 units when she had no more symptoms of shock and her diuresis had increased to 350 cc./day/M² (see chart 3). A tendency to increasing antidiuretic activity was seen during ACTH therapy which persisted in patients not showing a diuretic response after withdrawal of medication. In the present study there was no instance of a greater diuresis than that seen in the control cases. In a nephrotic child previously reported[8] a polyuric crisis of 5 l./day showed a chloride U/P ratio of 1, suggesting the role of ADH in the mechanism of some types of spontaneous diuresis and disappearance of edema seen in this renal condition. Determination of antidiuretic activity in fractionated plasma proteins, after washing out of precipitating salts, showed a normal effect (+6 rat unit) in the albumin fraction and +22 units in the globulin fraction from a nephrotic child that had previously shown +23 rat unit. No antidiuretic effect was caused by the protein-free filtrate or the ascitic fluid. The oliguric reaction of rats to pain from intraperitoneal injection of patient's serum was not seen in

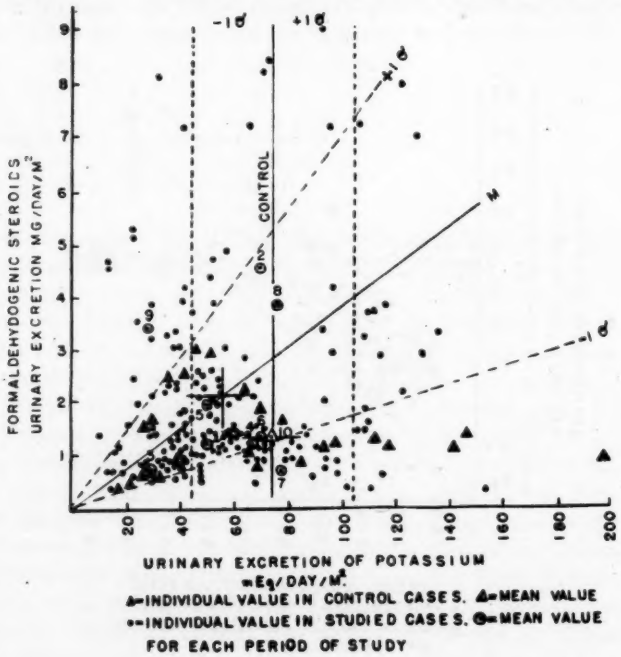

CHART 6.

animals receiving it from children during period of spontaneous elimination of edema. There were no striking changes in the urinary output of Na and Cl. No eosinophilic reaction was seen in rats immediately after injection of assay material and postmortem examination did not reveal any gross pathology of liver, kidney and cardiovascular system.

Additional Observations (see table 4): Eosinophile counts were done as an additional measure of adrenal function. Most cases showed a decrease of eosinophiles during bacterial infection and ACTH therapy, but otherwise no definite conclusion was drawn in relating steroids and eosinophile counts in regard to adrenal function. The same may be said about plasma constituents.

Renal function was markedly reduced in all nephrotic children and in the case of acute hemorrhagic nephritis as judged by clearance tests. Spontaneous increase in urinary volume with disappearance of edema did occur in four instances with a persistent reduction in the GFR and renal plasma flow (not included in this report). Diuresis induced by ACTH in one case increased the renal clearance of thiosulfate, urea and creatinine more than 100% but renal function did not reach the normal limit for children.

Potassium clearance was related to the decrease in the GFR in nephrotic children. The C_K/C_{in} ratio averaged 0.75 for nephrotic children and 0.78 for control cases. Sixty per cent of the simultaneous K and steroid observations in urine fell within ± 1 standard deviation of the plotted values for periods 1 to 9. Such correlation, however, seemed dependent on urinary volume, as it was not so for control cases (chart 6). Sodium excretion was very low through periods of study except during diuretic response to ACTH and CHPA.

Comment

Evaluation of adrenal function by urinary formaldehydogenic steroids could not be accurately done due to the influence of renal function on their excretion. Steroid excretion was related to diuresis in nephrotic children and it was not so in control children. Both nephrotic and normal children seemed to excrete steroids in relation to V/Cin and V/Cth ratio suggesting the participation of tubular reabsorptive processes in the urinary output of steroids. In the absence of any stimulating or depressing effect upon elaboration of steroids, urinary excretion during edematous and oliguric stage of nephrosis was not significantly different from that found in control cases. Stimulation of the adrenal cortex by ACTH in nephrotic children was not followed by a proportional increase in the urinary steroids. The excretion was usually higher in those showing a diuretic response. A decreased elaboration of adrenal steroids during spontaneous elimination of edema and increase in urinary volume and during CHPA therapy is suggested by its lower urinary output found in these two periods of study. Increase in urinary volume with disappearance of edema was found to occur with a high and a low urinary excretion of steroids; thus it seems probable that adrenal function did not directly participate in the onset of either spontaneous and induced increase of diuresis. Plasma steroids increased in all but one instance during ACTH therapy. A higher concentration than in control cases was also found in all but one instance during oliguria and edema (period 1). Plasma steroids decreased during spontaneous elimination of edema and no steroid in plasma was found in the case having shock and heart failure. Its plasma concentration seemed influenced by adrenal and renal functions and its diffusibility into the interstitial fluid.

A variable amount of formaldehydogenic material was found in ascitic fluid, its concentration being similar to that in plasma. The relative decrease of urinary excretion of

steroids during oliguria, and the rather large amount found in ascitic fluid suggests an excessive retention of steroids in the increased extracellular fluid of edematous nephrotic children. It seems probable that material found in ascitic fluid is mostly true steroids as it has been demonstrated that the formaldehydogenic nonsteroid substance present in blood does not pass through dialyzing membranes. If 11-desoxycorticosterone is one of the steroids present in the formaldehydogenic material, it may be accumulated in appreciable amount to account for some of the electrolyte and renal changes known to occur in nephrotic children and experimentally produced in animals by injection of DOCA.[46–48] This steroid was shown to be an original product of the adrenal cortex.[49] Though it was not found in the urine of normal individuals[50] a sodium-retaining steroid was reported to be present in the urine of nephrotic patients.[17]

Biologic tests in rats for evaluation of pituitary antidiuretic hormone (ADH) have been questioned.[10, 51] The arguments are solid enough for not claiming that the antidiuretic substance (ADS) present in the nephrotic sera is the result of an increased production of ADH. However, the ADS correlated to changes in diuresis in nephrotic children better than steroids in urine and blood. Increase in diuresis was usually preceded by or coincident with a decrease in the antidiuretic activity of nephrotic sera. Sudden changes in its activity were similar to the type described for ADH. The antidiuretic action was not the result of circulating steroids or ACTH. It was not the response to an antigen-antibody or an allergic reaction as demonstrated by the absence of eosinophilia and pathologic changes in the rat. An increased antidiuretic effect occurred with both an increased and a decreased urinary output of steroids. The ADS, regardless of its nature and source of production, was not present in ascitic fluid, plasma filtrate and albumin fraction. The oliguric response of rats to pain was not seen with serum from children having an increased diuresis. Most animals excreted a normal amount of Na and Cl in the urine. There was evidence that the ADS was present in the globulin fraction of plasma proteins of nephrotic children. More recently, Lauson, Forman, McNamara, Mattar and Barnett[52] found some antidiuretic effect of nephrotic sera injected into a child suffering from severe and untreated diabetes insipidus. The presence of ADS in nephrotic serum leads one to speculate concerning its relationship with other factors involved in antidiuresis, like STH,[53] VDM or ferritin[53–56] and renin.[57] Some of these factors have been found in increased amount in nephrotic patients.[53–57] The increase of ADS after injection of ACTH and its reversal on withdrawal of the hormone suggests the mediation of the neurohypophysis in the antidiuretic effect usually seen during initial doses of ACTH. Finally it may be that the effect of different stress factors upon both ADS and steroids in nephrotic children is the same as in normal individuals but the previous anatomic and physiologic status of renal tissue may determine an abnormal response reflected by an excessive retention of Na and H_2O, as well as an abnormal stimulus for the excessive elaboration of ADS. Events involved in diuresis are still poorly understood. Changes in renal hemodynamics and tubular transport mechanisms both participate, though a predominance of one is occasionally seen in studies on renal function as suggested by variations in renal blood flow, filtration rate, filtration fraction and U/P ratio. The authors have gained the impression from this study that changes in diuresis were more related to ADS than to steroids; that steroid excretion was enhanced after increase in urinary volume and that its retention in plasma and interstitial fluid occurred with the decrease in diuresis in nephrotic children. The independent elaboration of ADS and steroids may explain their role in different types of water and electrolyte diureses commonly seen in nephrosis. The improvement of renal hemodynamic by ACTH and corti-

sone therapy does not seem to be the only mechanism involved in their diuretic effect. These two hormones are known to exert an antagonistic action on adrenal cortical function, yet both induce a diuretic response in nephrotic individuals. Cortisone, however, causes a milder retention of water than ACTH and its influence in the production of ADS is still unknown.

Summary and Conclusions

The role of tubular reabsorption in the pathogenesis of nephrotic edema led the authors to study the participation of antidiuretic hormone and adrenal steroids in regard to changes in renal hemodynamics and tubular function during different clinical events that may induce an increase or a decrease of urinary flow in nephrotic children. Formaldehydogenic steroids in urine, plasma and ascitic fluid and serum antidiuretic substance were simultaneously studied with clearance tests, electrolyte excretion and plasma constituents through 10 different periods of observations.

From previous and present studies on renal function it was found that changes in renal hemodynamics and tubular transport mechanisms are responsible for variations in urinary flow leading to accumulation or disappearance of edema in the nephrotic syndrome. An increase in urinary flow was seen to occur with no change in the GFR but with a marked decrease in the U/P inulin and potassium ratio.

Serum antidiuretic substance appeared to correlate closely with antidiuresis. Injection of nephrotic sera into peritoneal cavity of rats was followed by an antidiuretic effect similar to that produced by pitressin and posterior pituitary hormone. Antidiuretic factor seemed to be present in the globulin fraction of plasma proteins. No such effect was seen with intraperitoneal injections of plasma albumin, protein-free filtrate and ascitic fluid. An increase in titer of antidiuretic substance was observed during initial doses of ACTH and the reverse at the onset of diuretic response.

Urinary excretion of formaldehydogenic steroids depended partly on diuresis in nephrotic children; this was not so in control cases. The influence of tubular function was suggested by the relationship found between urinary excretion of steroids and the V/Cin and V/Cth ratio and between clearance of steroids and diuresis. The influence of renal functional disturbance prevented a correct evaluation of adrenal activity by estimation of urinary steroids in nephrotic children. During the edematous-oliguric stage of nephrosis and in the absence of any stimulating or depressing effect upon the elaboration of adrenal steroids their urinary excretion was not significantly different from that seen in control cases. Formaldehydogenic steroids did not seem to have a direct role in producing variations of urine flow in nephrotic children. Increase and decrease in diuresis occurred simultaneously with an increase and a decrease in urinary and plasma steroids and vice versa.

Formaldehydogenic material was found in variable amounts in the ascitic fluid suggesting an appreciable retention in the increased extracellular fluid during the oliguric-edematous stage of the nephrotic syndrome. This material appears to be mostly true adrenal steroids.

Potassium excretion was related to urinary steroids in nephrotic children but not in control cases. Potassium clearance was related to glomerular filtration in both control and nephrotic children.

At the present time it remains a matter of some speculation of the role that steroids present in extracellular fluids may play in the physiologic and morphologic changes known to occur in the course of the nephrotic syndrome and experimentally reproduced by injection of DOCA to animals.

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SPANISH ABSTRACT

Corticosteroides y Substancias Antidiuréticas en el Síndrome Nefrotico en Niños

El role de la hiperreabsorción tubular en la patogenia del edema nefrósico nos llevó a estudiar la participación de la hormona antidiurética y de los esteroides suprarenales en los cambios de la hemodinámica y función tubular durante distintos eventos clínicos que son susceptibles de inducir un aumento o disminución de la diuresis en niños nefrósicos. En el curso de diez períodos distintos de observación se estudiaron simultaneamente los esteroides formaldehidogénicos en la orina, plasma y líquido ascítico, la substancia antidiurética del suero, la función renal, la excreción de electrolitos y los constituyentes del plasma.

En estudios previos de la función renal observamos que los cambios en la hemodinámica y en la función de transporte tubular son ambos responsables de las variaciones de la diuresis que pueden conducir a la formación o desaparición del edema nefrósico. Se observó un aumento del flujo urinario sin cambios en la filtración glomerular previamente reducida pero con una marcada disminución del índice de concentración U/P para la inulina y el potasio.

Las variaciones en la actividad de la substancia antidiurética del suero mostraron una relación estrecha con los cambios de la diuresis. La inyección de suero nefrótico en la cavidad peritoneal de la rata fué seguida de una respuesta antidiurética semejante a aquella provocada por el pitressin y la hormona del lóbulo posterior de la hipófisis. El factor antidiurético pareció estar presente en la fracción globulínica del suero. Este efecto no ocurrió con inyecciones intraperitoneales de seroalbúmina, filtrado libre de proteina ni con líquido ascítico. Se observó un aumento en el título de la substancia antidiurética del suero durante las dosis iniciales de ACTH y una disminución al comienzo de la respuesta diurética.

La excrecion urinaria de esteroides formaldehidogénicos en el niño nefrósico dependió grandemente de la diuresis. Esto no fué observado en los casos de control. La participación de la función tubular en la excreción urinaria de esteroides parece demostrarse por la relación hallada entre ésta y el índice V/Cin y V/Cth así como por la relación entre el aclaramiento de esteroides y la diuresis. La interferencia producida por la perturbación funcional del riñón no permitió una valoración correcta de la función suprarenal mediante la determinación de los esteroides en la orina.

Durante el periodo oligúrico-edematoso de la nefrosis y en ausencia de todo efecto estimulante o deprimente en la elaboración de los esteroides, la excreción urinaria de éstos no mostró una diferencia significativa con la observada en casos de control. Los esteroides formaldehidogénicos no mostraron una participación directa en las variaciones de la diuresis en los niños nefrósicos. Se observó, en efecto, un aumento y disminución en la diuresis conjuntamente con un aumento o disminución de los esteroides y viceversa.

Encontramos una cantidad variable de material formaldehidogéníco en el líquido ascítico, que sugiere una apreciable retención de los esteroides en el líquido extracelular aumentado, durante la fase oligúrica-edematosa de la nefrosis. Este material parece estar mayormente formado por esteroides verdaderos.

La excreción urinaria de potasio mostró una relación con los esteroides urinarios en los niños nefrósicos pero no en cos casos de control. Su aclaramiento pareció depender de la filtración glomerular tanto en los niños controles como nefrósicos.

En el presente momento es motivo de especulación el role que los esteroides hallados en los líquidos extracelulares puedan jugar en ciertos cambios morfológicos y fisiológicos que sabemos ocurren en la nefrosis y que pueden ser reproducidos por la inyección de DOCA a animales de experimentación.

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UNTOWARD EFFECTS OF ENEMATA IN CONGENITAL MEGACOLON

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EPISODES of syncope varying from mild shock to rapid collapse and death frequently follow the administration of enemata in patients with congenital megacolon, particularly when the solution used is water, and when one of the parasympathomimetic drugs is given coincidentally. Such reactions have been previously described by one of the authors (R. B. H.) and were found to occur in approximately 60% of a series of 42 cases.[1]

A review of the literature on congenital megacolon for the past 10 years discloses little information on the subject, and no reports or warnings are to be found in the pediatric literature or textbooks. The striking improvement in the prognosis of this disease which has followed advances in surgical treatment makes general knowledge of this complication imperative in order that these tragic accidents may be prevented. For this reason a review of the subject and some illustrative case reports are presented.

REVIEW OF THE LITERATURE

Wesley[2] stated that children with achalasia of the lower bowel occasionally suffer from collapse while attempting to defecate, but gave no opinion concerning the frequency or mechanism of this phenomenon. Moncrieff and Crichlow[3] reported a case of congenital megacolon (Hirschsprung's disease) in a patient who died suddenly after one week of increasing abdominal distension, during which time enemas had been productive of "poor results." Postmortem examination revealed semifluid feces in the entire colon, but no cause of death was discovered. Whitehouse and Kernohan[4] in an excellent review of the microscopic pathology of the colon in this disease reported 11 postmortem examinations. Most of the deaths were operative or postoperative fatalities, but three children are of interest as possible examples of sudden death of the type under discussion. One of these ". . . died suddenly within a few hours of the first signs of an unknown toxicity." Another, admitted to a hospital for relief of fecal impaction, failed to respond during three days of medical management and died, presumably of weakness and debility. The third died suddenly with elevated pulse and temperature after five days of hospitalization, and autopsy failed to reveal the cause of death.

Burnard[5] discussed the outcome of congenital megacolon in infancy. Twenty-three patients were studied, and of these 18 had died at the time of writing. One patient died suddenly at 4 years of age, autopsy revealing the characteristic lesion of the colon, but not the cause of death. In two other cases the author stated "death was sudden and for no obvious cause." Four other patients died at home soon after hospital discharge, one of these "during an attack of bronchitis." It is conceivable that some of these deaths were due to reactions to enemata.

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Jolleye[6] has recently reported the death of a 4 year old child following the administration of 2.3 l. of a barium solution (suspending agent not stated), and 850 cc. of a soapsuds solution given subsequently in an attempt to recover the retained barium enema. This child on return to the ward was cold, perspiring, and in shock, and vomited dark-colored fluid. Seven hours later coma, cyanosis, convulsions and polyuria (sp. gr. 1.001) were noted. Death occurred in a convulsion 20 hours after instillation of the barium solution. Autopsy was not performed. The barium mixture was analyzed, and no soluble barium salt was found. The author concluded that the cause of death was "water intoxication," and advised treatment of such reactions with intravenous injection of hypertonic sodium chloride solution.

The following typical cases are reported to illustrate the nature and emphasize the danger of this complication. All were known cases of congenital megacolon verified by roentgen examination or subsequent surgery.

Case Reports

Case 1. V. D., a girl 4 yr. of age, was admitted to hospital in 1948. Hers was the first severe reaction encountered. On 1st 2 hospital days she received 2 large colonic lavages of unstated composition and a soapsuds enema. Early in morning of 3rd hospital day she was found convulsing and unconscious. There was no response to calcium gluconate or phenobarbital therapy. Because of extreme abdominal distension 7.7 l. of tap water were given by colonic lavage, with return of brown fecal material. One hour later she was cyanotic, and 2 hr. later frothy bloody material was noted to be exuding from mouth; she died 10 min. later. From outset she convulsed continuously. Postmortem examination revealed following findings: brain—congestion of leptomeninges, flattened convolutions and narrowed sulci, and symmetric reduction in size of lateral ventricles. Lungs—extreme pulmonary edema. Colon—3.2 l. of fluid present, typical congenital megacolon.

Case 2.* L. V., a boy 3 yr. of age, was discharged from hospital, after confirmation of clinical diagnosis of congenital megacolon by RG, on a medical regime consisting of prostigmine (0.5 gm. b.d.) and enemata as required. Response was good initially, but constipation recurred after 1 mo. A soapsuds enema was given and was retained. Then a dose of prostigmine was administered. About 1 hr. later, while the patient was straining to defecate, he frothed at mouth, rapidly lapsed into coma, and was rushed to a local physician's office, where he was found to be dead on arrival. Autopsy was not performed.

Case 3. K. F., a boy 6 yr. of age with megacolon, suddenly complained of pain in throat following hypodermic injection of prostigmine 0.045 gm. and administration of a soapsuds enema of unstated quantity in hospital. He then began to vomit and said that he could not see. Physical examination revealed a pale retching child with cold extremities and colicky abdominal pain. Blood pressure was 60/20 mm.Hg and 5 min. later, after hypodermic injection of atropine sulfate 0.0001 gm., had risen to 90/60 mm.Hg. He was quieter at this time, and gradually recovered spontaneously.

Case 4. R. K., a boy 15 mo. of age, was being treated at home on a medical regime consisting of prostigmine and enemas as needed. During a colonic irrigation (solution unstated) he became irritable, cyanotic and pulseless, coughing unproductively and gagging repeatedly. In course of next 2 days colonic irrigations were given without event. On 3rd day, during an irrigation, the patient cried out hoarsely, started to "choke up," became weak, pale and pulseless. Irrigation was stopped, whereupon spontaneous recovery occurred. The following day, local physician attended the irrigation; he later stated that during it patient suffered an episode of pulmonary edema, manifested by moist rales and cyanosis. Parents discontinued both prostigmine and irrigations temporarily, but several days later, because of increasing abdominal distension, patient was given 2 doses of prostigmine and another irrigation, whereupon he had another episode of shock. On suspicion that he was suffering from prostigmine toxicity, an injection of atropine sulfate was given; this was thought to improve his condition.

Case 5. P. F., a boy 2 yr. of age, was being treated at home with enemata and a combination of prostigmine and syntropan®. Following an enema consisting of 350 cc. of a sodium bicarbonate

* Case report obtained through courtesy of Dr. Sidney Robin, Chicago.

solution, mild shock occurred, which responded rapidly to home treatment. About 2 mo. later a 400 cc. soapsuds enema was given 3 hr. after usual administration of prostigmine and syntropan®; 15 min. later cyanosis was noted, and within 30 min. patient lost consciousness. He was taken to a neighborhood hospital, where he responded within 3 hr. to an intravenous infusion of plasma and other fluids.

While this patient was being prepared for surgery in hospital, serial determinations of plasma electrolyte concentrations were made after the instillation of a tap water enema (400 cc.), as previously described.[1] One hour and 20 min. after the enema, serum Na had fallen from 137.5 mEq./l. to 127.5 mEq./l.; plasma protein from 8.06 gm./100 cc. to 7.09 gm./100 cc.; and plasma specific gravity from 1.0286 to 1.0261. No clinical reaction accompanied these chemical alterations, and the solution of hypertonic sodium chloride solution which had been held in readiness was not needed.

Case 6. G. F., a boy 4 yr. of age, was given in course of home treatment an enema consisting of a solution of borax in water, total volume thought to be less than 1 qt. A few minutes later he became nauseated and vomited several times, and after about 30 min. was found to be cold and clammy. He was seen by a local physician at a hospital some hours later, who stated that he had suffered a sudden episode of prostration which responded to treatment with plasma, external heat and intravenous infusion of glucose and saline solutions.

Case 7. D. C.,* a girl 6 yr. of age, received a tap water enema of unstated amount after which she evacuated a small amount of liquid fecal material. Three hours later her abdomen was noted to be hard, and she began to urinate frequently and in large quantities. Four and one-half hours after 1st enema, another enema consisting of cane sugar 60 gm. and $NaHCO_3$ 60 gm. dissolved in tap water 200 cc. was given, with production of a large amount of gray-black, formed stool. Patient then vomited and complained of headache, and skin became cold and clammy. Irritability and weakness developed, and about 10 min. after 2nd enema she lapsed into coma and displayed signs of a tonic convulsion (teeth clenched, eyes externally rotated). Blood pressure was 120/45 mm.Hg, PR 140/min. at this time. She remained in a restless coma for about 2½ hr., during which time there was a practically continuous flow of gray fecal material and liquid from anus. She then recovered spontaneously, complained of thirst, and took fluids eagerly during following 12 hr.

Case 8. N. R., a girl 6 yr. of age, while in hospital was given an enema consisting of soapsuds solution 700 cc. after which she expelled a large amount of feces and fluid. Shortly thereafter she became cold and clammy, and appeared to be in shock. Blood pressure was 84/34 mm.Hg and slowness of response to stimuli was noted. Abdomen was rigid and tender, but roentgen films of abdomen did not show presence of free air. Spontaneous recovery occurred.

Case 9. R. B., a boy 4 yr. of age, was hospitalized for operation. At time of admission mother volunteered information that patient had fainted occasionally after enemas with soapy water, but that since she had been using oil enemas no reactions had occurred.

Discussion

The clinical picture demonstrated by most of these patients, characterized initially by weakness, headache, vomiting and cough, and eventually by pallor, perspiration, polyuria, coldness of the skin, syncope, and sometimes death in coma and convulsions, is best explained by the syndrome of water intoxication. Case 1 is similar in all respects to the classical description of the first fatal human case by Helwig et al.[7] The pathophysiology is apparently altered function of essential structures, particularly the central nervous system, caused by a sudden increase in intracellular water content.

This pathogenesis is supported by the fact that in all the cases reported here where the enema composition was known, water or aqueous solutions having low osmotic pressure (e.g., soapsuds solutions) were the inciting agents. Further corroboration is offered by the postmortem findings in Case 1 and by the chemical determinations in Case 5. The sudden and unexpected nature of the reactions described accounts for the lack of

* Case report through courtesy of Children's Memorial Hospital, Chicago.

laboratory documentation. One is more concerned with promoting recovery of the patient in syncope than with experimental studies of water balance, and no animal preparation simulating the conditions of congenital megacolon is available for experimental work.

Although water intoxication appears to explain the majority of the reactions described, there is reason to suspect that additional etiologic factors were operative in some of the cases. The most important of these is prostigmine intoxication, of which Cases 3 and 4 are probably examples. The symptoms of overdosage with this drug are similar to those of water intoxication, except for the presence of pin-point pupils, blurring of vision and dyspnea, and the absence of coma except as a terminal event. Absorption of this drug from the alimentary tract, though normally poor, could conceivably be greatly enhanced by the combination of stasis of intestinal contents and hypertrophy of the colonic mucous membrane. In addition to the direct toxicity of large doses of prostigmine, doses in the physiologic range probably facilitate absorption of hypotonic enema solutions by producing peristaltic contractions of the colon and increased hydrostatic pressure within the lumen.

Other factors which may have played a role in these reactions were the use of alkaline solutions (Cases 6 and 7), the potential toxicity of sodium borate if absorbed (Case 6), and the direct irritative effect of the strongly hypertonic solution used in Case 7. This patient developed signs of water intoxication (abdominal rigidity and marked polyuria) from the hypotonic enema given prior to the administration of the hypertonic alkaline enema; it is possible that the latter solution created an osmotic gradient which drew the excess extracellular fluid back into the colon, thereby bringing about a state of dehydration. This speculation cannot be proved, but is supported by the presence of thirst and polydipsia in the recovery phase.

Further evidence favoring the increased absorptive powers of the mucosa in congenital megacolon is provided by the report[8] of a fatality with clinical and laboratory findings of magnesium intoxication following the administration of a small magnesium sulfate enema in a patient with this disease. Although such enemas have been given without mishap in many patients with megacolon, the authors stress the increased permeability of the diseased gastrointestinal membrane, and state that magnesium sulfate enemas are contraindicated in patients with primary megacolon. In contrast to this report, routine use of magnesium sulfate retention enemas has been recently advocated,[9] although rare instances of shock following administration of such an enema and the evacuation of a large amount of fecal material are stated to occur.

Prophylaxis

1. Water Intoxication: As early as 1941, Soper[10] recommended the use of 10% sodium sulfate as an enema solution, because it would stimulate contractions without being absorbed by the mucosa. The present authors' experience indicates that enemas consisting of isotonic sodium chloride solution can be given in large amounts with impunity in the absence of renal or cardiac lesions, since the absorption which occurs only results in an increase in extracellular fluid without serious dislocation of the electrolyte pattern, and is readily compensated by normal kidneys. However, an isotonic solution of an inert substance, such as gelatin (7%), would probably be preferable for routine use because of its safety, and should certainly be employed when renal or cardiac disease is present to prevent pulmonary edema.

Barium salts used in enemas for diagnostic purposes in suspected cases of this disease should be suspended in isotonic sodium chloride solution rather than in water.

Rational therapy of an established attack would seem to be the immediate intravenous injection of hypertonic (2%) sodium chloride solution.

2. Prostigmine Intoxication: Dosage of this drug in patients with congenital megacolon should be smaller than that usually recommended. Such a reduction would probably be wise in the case of any potentially toxic drug which is given orally in many times its parenteral dose in anticipation of poor absorption from the gastrointestinal tract.

3. Potentially toxic substances such as magnesium sulfate or borax used in enema solutions are contraindicated in patients with congenital megacolon.

Summary

The problem of untoward reactions to enemata in cases of congenital megaclon has been discussed, and nine cases of such reactions presented. The evidence, although admittedly incomplete, seems to favor water intoxication as the basis of most of these reactions. Other possible etiologic factors are discussed.

A routine for the prevention of syncope by the use of isotonic enema solutions in cases of congenital megacolon is advocated. The use of tap water or soapsuds enemas or of solutions containing potentially toxic substances such as magnesium sulfate is contraindicated in congenital megacolon.

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Spanish Abstract

Reacciones Desagradables con el Empleo de Enemas en el Megacolon Congénito

Con mucha frecuencia la administración de enemas a pacientes con megacolon congénito se acompaña de síncope, variable de shock ligero a colapso o muerte, en particular cuando la solución es acuosa y el enfermo está recibiendo una de las substancias parasimpatico-miméticas. Pocos informes se tienen al respecto en los últimos diez años; el pronóstico de este padecimiento, tan favorable con el tratamiento quirúrgico, hace obligatoria la difusión de estas complicaciones para evitar accidentes trágicos.

Los autores presentan nueve casos de niños en quienes se presentaron diversos cuadros clínicos tras el uso de enemas; se iniciaban generalmente por debilidad, cefalea, vómitos y tos, seguidos más tarde de palidez, sudoración profusa, poliuria, piel fría, síncope y en ocasiones muerte en coma y

convulsiones; el cuadro era el del síndrome de intoxicación por agua. Suponen que la fisiopatología radica aparentemente en alteraciones funcionales de estructuras esenciales, particularmente en el sistema nervioso central, provocadas por el aumento brusco del contenido acuoso intracelular. Otros factores que deben tomarse en cuenta son: la intoxicación por prostigmina, cuya absorción generalmente escasa en el tracto digestivo, podría acentuarse tanto por la estasis del contenido intestinal como por la hipertrofia de la membrana mucosa del colon; el empleo de enemas con soluciones alcalinas, la toxicidad potencial del borato de sodio y por último el efecto directo irritativo de las soluciones altamente hipertónicas.

La profilaxis de estas reacciones tan desagradables debe dirigirse hacia la prevención de la intoxicación por agua y por la prostigmina así como la proscripción del empleo de enemas de substancias potencialmente tóxicas como el sulfato de magnesio y borato de sodio, en soluciones hipertónicas, substituyéndolas por soluciones isotónicas.

630 West 168th Street

ON THE POSSIBLE INFLUENCE OF GREAT ALTITUDES ON THE DETERMINATION OF CERTAIN CARDIOVASCULAR ANOMALIES

Preliminary Report

By VÍCTOR ALZAMORA, M.D., ANDRÉS ROTTA, M.D., GUIDO BATTILANA, M.D., RICARDO ABUGATTAS, M.D., CARLOS RUBIO, M.D., JOSÉ BOURONCLE, M.D., CÉSAR ZAPATA, M.D., E. SANTA-MARÍA, M.D., TODORO BINDER, M.D., RICARDO SUBIRIA, M.D., DAVID PAREDES, M.D., BENJAMÍN PANDO, M.D., AND GEORGE G. GRAHAM, M.D.

Lima, Peru

STUDIES carried out by Peruvian and other observers have demonstrated the influence on the human race of prolonged stay at high altitudes. There have been numerous publications on the biologic, clinical, radiologic and electrocardiographic peculiarities of the heart of the inhabitant of the Andean heights.[1-5] Some preliminary observations suggest that prolonged stay at great altitudes has some influence on the development of the animal germ plasm.[6,7] The present study deals with the effect that the altitude seems to have on the determination of certain anomalies of the heart.

OBSERVATIONS

The first three congenital anomalies of the heart diagnosed in 1944 in the Cardiology Outpatient Department of this hospital were two cases of patent ductus arteriosus and one of interatrial septal defect (two of them verified at autopsy), and it was noticed that all three had been born in the mining center of Cerro de Pasco or nearby at an altitude over 4,000 meters. Since that time, in order to find out if this was a fortuitous occurrence, in each case of cardiac anomaly the exact place of birth was determined, as well as the length of stay thereafter. After eight years the authors have some suggestive figures.

Ten thousand clinical histories from the Outpatient Department as well as from the private practice of one of the authors (V. A.) yielded 176 cases of cardiac anomaly. The diagnoses were based on clinical, radiologic and electrocardiographic observations; in many cases the circulation time was determined, and in some, information was obtained by catheterization of the right heart and angiocardiography. In 17 cases the diagnosis was confirmed at operation (15 patent ductus arteriosus and 2 tetralogy of Fallot), and in 8 cases at autopsy (2 patent ductus arteriosus, 3 interatrial septal defects, 2 interventricular communications and one Lutembacher syndrome).

Patients from the Out-patient Department, in contrast with private practice, are always adult males of modest means, largely *mestizos,* and since this service has provided over half the cases, little importance can be attached to the statistical significance of the age, sex and race of this group. On the other hand, the geographic location of the Outpatient

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Department and the large current of migration to Lima from the rest of the country make this a fairly representative sample.

In order to establish the validity of the suggestive observations, an effort was made to show whether these figures could have occurred by chance.

The place of birth of 1,000 consecutive admissions to this service was determined and from there the authors calculated the percentage of patients from each locality that were to be expected in each group.

It was found that 42.4% of this were born in the department of Lima, which includes Lima (39.3%), while only 6.9% were born in the departments of Junin and Pasco together, which includes the towns of Cerro de Pasco (1.7%), La Oroya (0.4%) and Morococha (0.1%). The vast majority of the remaining patients were born in other sections of the country whose maximum altitude seldom exceeds 3,000 meters, so that it can easily be said that no more than 15% of the patient population in this clinic should have been born above that altitude, no more than 9% above 3,500 meters, and certainly no more than 3% above 4,000 meters.

The fact that most of the patients were adults tends to lower the relative incidence of those malformations most likely to cause death in infancy and childhood, and consequently, the figures in this group are far from representative.

Results

The 176 cases of cardiac anomaly have arbitrarily been divided into six groups.

1. Miscellaneous: thirty-nine cases, including dextrocardia, cardiopathies with cyanosis and abnormalities of the aortic arch. The authors could establish no correlation with altitude in this group.

2. Interventricular Communication: 29 cases. The places of birth of this group were widely scattered with no relation found to altitude.

3. Coarctation of the Aorta: 7 cases. In all of these the diagnosis was clear and only one was born above 3,500 meters, in Cerro de Pasco. This group is too small for any valid observation.

4. Pulmonary Stenosis: 8 cases. Here the diagnosis is only presumptive as none of these cases were catheterized or explored. However, 3 of the 8 were born above 4,000 meters. This, though suggestive, is not significant.

5. Interatrial Communications: 51 cases. The clinical diagnosis in this group can be made with a fair degree of exactitude. Of the 51, 9 (17.7%) were born above 4,000 meters and 4 more (7.8%) between 3,500 and 4,000 meters. This is significantly more than might have been expected.

6. Patent Ductus Arteriosus: 42 cases. This includes only cases with a clearcut clinical diagnosis, or proved at operation* or necropsy. It is interesting to note that not one of these cases came because of or had any signs of superimposed endocarditis. Of the 42 cases, 13 (30.9%) were born more than 4,000 meters above sea level, 5 (11.9%) between 3,500 and 4,000 meters and 8 (19.0%) between 3,000 and 3,500 meters. For all these altitudes, the differences between the expected and observed number of cases is statistically significant.

Discussion

These figures indicate that a patent ductus arteriosus or interatrial defect is more likely

* Performed by Dr. C. A. Peschiera.

to be found in a subject born at high altitudes. It remains to be shown that this is true for other defects, particularly anomalies of the pulmonary artery. There is no reason to believe that rubella is more common at these altitudes and the few mothers who could be interviewed denied any history of eruptive illness during the pregnancy in question. Racial factors seem to have no influence in these figures.

The obliteration of the ductus arteriosus, as all morphogenetic processes, is due to various causes, not all of which are understood. It is presumed that in the first moments after birth a "functional" obliteration takes place because of an equilibration of the pressure at the pulmonary and aortic ends,[8] due mostly to the initiation of respiration. It is interesting to note that Senac, in 1749, believed that the ductus arteriosus remained patent when respiratory function was impeded.[9] The experimental work of Kennedy[10] allows the supposition that oxygen is the major stimulus to this obliteration, acting even when injected through the umbilical vein. He has apparently demonstrated that pulmonary expansion by an inert gas is ineffective, but that obliteration takes place when the oxygen concentration is adequate.

The authors do not know what the intimate cause for the frequent persistence of the ductus arteriosus at high altitudes may be, but it seems probable that the mechanical factor in the pulmonary circulation as well as the oxygen tension are responsible.

It may be mentioned that functionally, at least, the foramen ovale behaves in many respects like the ductus arteriosus and that its anatomic obliteration often takes place months after birth.

It seems that the effect of high altitudes becomes clearly manifest at 3,000 meters or over.

Summary

Over a period of 8 years, 176 cases of cardiac anomalies have been found in over 10,000 consecutive admissions. The place of birth and its altitude have been recorded for each one of these causes.

Patent ductus arteriosus and persistent interatrial communications are more likely to be found in patients born at high altitudes.

It is suggested, but remains to be shown, that this is true for defects of the pulmonary artery. No apparent relation could be found in this series for other malformations.

It is presumed that mechanical factors tied to the pulmonary circulation and the lower oxygen tension both have a decisive influence.

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SPANISH ABSTRACT

Influencia Probable de las Grandes Altitudes Sobre la Determinación de Algunas Anomalías Cardiovasculares

Los autores han encontrado 176 casos de anomalías cardiacas en más de 10,000 admisiones consecutivas en un período de 8 años; el lugar de nacimiento y su altitud se han anotado para cada uno de estos casos. La persistencia del conducto arteriovenoso y la de las comunicaciones interauriculares se encuentran con mayor frecuencia en los nacidos a grandes altitudes; se sugiere que lo mismo pasa con los defectos de la arteria pulmonar aunque falta demostrarlo.

No han encontrado en esta serie ninguna relación aparente con otras malformaciones.

Se supone que tienen influencia decisiva los factores mecánicos debidos a la circulación pulmonar y la tensión más baja de oxígeno.

British American Hospital

SOME EFFECTS OF EXOGENOUS THYROID OR THYROXIN UPON PREMATURE INFANTS

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GUDERNATSCH[1] showed that the metamorphosis of the tadpole could be stimulated by thyroid medication and Moncrieff[2,3] presented data to suggest that premature babies, given a daily dose of thyroid extract 3.0 mg./0.5 kg., are easier to feed and to keep warm and have a lower mortality rate. No definitive work has been reported since Moncrieff's experiment in 1938 but the possibility of improving the postnatal development of premature infants by thyroid medication has continued to intrigue clinicians. The present paper reports observations on some effects of exogenous thyroid or thyroxin upon 24 premature infants who are compared with 24 alternate control premature babies.

MATERIALS AND METHODS

Premature infants born at the Elizabeth Steel Magee Hospital, whose birth weights approximated 1500 gm. and who presented no abnormality, were selected for observation. The care and medication of all these babies were supervised directly by the head nurse of the premature nursery.

Odd-numbered infants in the series so selected were given the contents of red gelatin capsules or small yellow pills. Even numbered infants were given the contents of colorless gelatin capsules or small white pills. There were no exceptions to this regimen. In the event of multiple birth where both twins were premature, A and B were treated as consecutive infants in the series. The number of capsules or pills given daily varied from 1 to 3, depending on dosage desired, but number and type of vehicle were always the same for concurrent control and study infants. The red capsules and yellow pills contained lactose. Each colorless capsule contained 60 mg. desiccated thyroid U.S.P. from the same lot number.* Each white pill contained 0.1 mg. L-thyroxin.† No one working with the infants knew which capsules and pills contained placebos.

Medication was placed in a sterile medicine glass and ½ oz. of the standard feeding mixture was added. After thorough agitation of the contents of the glass the resulting suspension was fed to the infant with a medicine dropper. Another ½ oz. of standard feeding mixture was then added to the empty glass, the contents agitated and fed with the same medicine dropper. This medication was given just before the 3 P.M. feeding and was followed by the prescribed feeding minus 1 oz. No unusual regurgitation resulted and the method of administration assured that the calculated dose was swallowed. Medication was started when an infant had attained a daily caloric intake which was adequate to produce gain in weight. Placebo medication was begun on the control infants at an average age of 10 days and an average weight of 1670 gm.; thyroid or thyroxin medication was begun on the study infants at an average age of 8 days and an average weight of 1590 gm. Control infants were treated for an average period of 25 days and study infants for an average period of 26 days. Daily medication was continued, except as noted, until each infant weighed approximately

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† Elthrin®, supplied through the courtesy of Smith, Kline and French Laboratories.

2500 gm. The babies were usually discharged within 2 to 5 days after this achievement and no follow-up was made.

The control series consisted of 5 males and 19 females, 16 whites and 8 Negroes. In the study group there were 11 males and 13 females, 13 whites and 11 Negroes.

Prematurity of the control infants was attributed to multiple birth (8), premature rupture of membranes (2), eclampsia (1), maternal rheumatic heart disease (1), placental accident (1) and cause unknown (11). Prematurity of the study infants was related to multiple birth (9), premature rupture of membranes (6), placental accident (3) and cause unknown (6). There were 5 twin births where both twins were premature.

Notes on infants in this study were kept on separate work sheets. Temperature and pulse extremes, number and consistency of stools, ounces of feeding mixture ingested, medication (in terms of capsules or pills) and comments on skin color, gavage feeding, regurgitation, infections, parenteral fluids, blood transfusions, etc., were recorded daily. Body weight was recorded every other day. Red cell counts and hemoglobin levels (Haden Hauser: 15 gm. = 100%) were determined at weekly intervals. Blood was withdrawn once a week for protein-bound iodine determinations and the sera were analyzed usually in duplicate by the method of Barker, modified.[4,5]

Infants were kept in Gordon Armstrong Portable Baby Incubators whose temperatures were regulated from 35°C. for the smallest babies to 27°C. for the largest ones. Oxygen flow was at the rate of 6 l./min. When an infant reached a weight of approximately 2300 .gm., the incubator was opened slowly to a room temperature of 24°C. and a humidity of 50 to 60%.

The following feeding regimen was employed:

1st day—nothing by mouth

2nd day—5% glucose, 1 oz. q.3h. as tolerated

3rd and 4th days—½ strength standard feeding mixture, 1 to 2 oz. q.3h. as tolerated

5th day—begin standard feeding mixture—Dryco® 16 T
(21 cal./oz.) Karo 3 T
Water 32 oz.

Increase this mixture cautiously as tolerated and as indicated by infant's hunger or failure to gain weight.

Ascorbic acid—100 mg. daily, beginning 3rd day

Poly-vi-sol®—0.3 cc. daily, 3rd to 14th day
0.6 cc. daily, beginning 15th day

Infants are given parenteral fluids, gavaged, and receive extra oxygen by funnel (3 l./min.) as clinically indicated.

Results

A. Observations on Intake, Vomiting, Skin Color and Body Temperature.

Control infants consumed an average of 309 calories (14.7 oz.) and study infants an average of 305 calories (14.5 oz.) in each 24 hours during the period of observation. Six of the 24 control infants (25.0%) and 7 of the 24 study infants (29.2%) were gavaged for one or more days during the period of observation. These amounts and percentages do not differ significantly. Five of the 24 control infants (20.8%) and 6 of the 24 study infants (25.0%) vomited amounts which were considered abnormal. The control infants vomited during 10 of the 609 observation days (1.6%) and the study infants vomited on a total of 9 of the 626 observation days (1.4%). These percentages do not differ significantly. Transient pallor or slight circumoral cyanosis was occasionally noted. Such observations were rare, however, and did not differ significantly in the two groups. No differences in the degree or fluctuation of body temperature were evident between the control and study infants.

As indicated earlier, each of the five pairs of twins was divided into a control and a study infant. No significant differences were observed in progress except that the larger twin, whether control or study, always showed a larger average daily weight increment.

Three infants were given a daily dose of thyroid 60 mg. for an average period of 19 days. They did not differ significantly in any observed respect from the control infants and are not presented in the tables.

B. Weight Gain.

Table 1 shows that the infants who were given a daily dose of thyroid 180 mg. or thyroxin 0.2 mg. achieved an average daily weight increment of 30 gm. The control infants gained an average of 36 gm. per day. These differences are significant ($t = 2.0$ and 2.4, respectively). Daily dosage with thyroid 120 mg. was without significant effect on weight gain which averaged 34 gm. per day for this group. One control infant suffering from diarrhea, whose treatment with placebo was discontinued after 7 days, is not included in this table.

TABLE 1

Type of Treatment	No. infants	Mean Gain ± S E. (gm./day)
Control	23	36±1.4
Thyroid 120 mg./day	6	34±2.0
Thyroid 180 mg./day	6	30±1.1
Thyroxin 0.2 mg./day	9	30±1.4

C. Diarrhea Incidence.

In this study, an infant was considered to have diarrhea when he passed abnormally liquid stools for two or more days. Study infants show an incidence as high as 50.0% as compared with 8.3% for the control infants. The magnitude of the percentage differences is impressive although the numbers involved are too small for statistical analysis. (See table 2.)

TABLE 2

Type of Treatment	No. infants	No. infants with diarrhea	% infants with diarrhea
Control	24	2	8.3
Thyroid 120 mg./day	6	1	16.7
Thyroid 180 mg./day	6	3	50.0
Thyroxin 0.2 mg./day	9	4	44.5

D. Pulse Rate.

Table 3 shows that the infants who were given a daily dose thyroid 180 mg. and the infants who were given a daily dose of thyroxin 0.2 mg. had average pulse rates of 175 and 173. The control infants averaged 163. These differences are significant ($t = 2.7$ and

TABLE 3

Type of Treatment	No. infants	Mean Pulse rate ± S.E.
Control	24	163 ± 1.5
Thyroid 120 mg./day	6	162 ± 4.2
Thyroid 180 mg./day	6	175 ± 3.5
Thyroxin 0.2 mg./day	9	173 ± 2.1

3.4, respectively). Daily dosage with thyroid 120 mg. was without significant effect upon the pulse rate which averaged 162 for this group.

E. Transfusion Incidence.

Table 4 shows that 16.7%, 33.3% and 44.5%, respectively, of the study infants in the three dosage groups were transfused with whole blood as compared with 4.2% of

TABLE 4

Type of Treatment	No. infants	No. infants transfused	% infants transfused
Control	24	1	4.2
Thyroid 120 mg./day	6	1	16.7
Thyroid 180 mg./day	6	2	33.3
Thyroxin 0.2 mg./day	9	4	44.5

the infants in the control group. The consistency and the magnitude of the percentage differences are noteworthy although again the numbers are too small for statistical analysis.

Table 5 shows average red cell counts and hemoglobin levels of all groups of infants before treatment, the lowest average values recorded for each group of infants during the

TABLE 5

RED CELL COUNTS AND HEMOGLOBIN LEVELS

Type of Treatment	RBC before treatment	Lowest RBC	Drop in RBC	Hgb./100 cc. before treatment	Lowest Hgb./100 cc.	Drop in Hgb./100 cc.
Control	4.50	3.08	1.42	90	63	27
Thyroid 120 mg./day	4.53	3.43	1.10	91	69	22
Thyroid 180 gm./day	4.32	2.63	1.69	86	54	32
Thyroxin 0.2 mg./day	4.10	2.91	1.19	82	60	22

period of observation and the differences between the initial and the lowest readings. The infants who were given daily doses of thyroid 180 mg. or thyroxin 0.2 mg. developed the lowest average red cell counts and hemoglobin levels. Their initial average values, however, were lower and the differences between their initial and lowest levels approximate those of the control group.

F. Fate of Infants.

As already mentioned, one control infant developed severe diarrhea after 7 days of observation and at a weight of 1750 gm.; medication was then stopped and he recovered. One suffered a cellulitis of the right thigh which was successfully treated with penicillin and streptomycin and one had a persistent systolic murmur.

One study infant died of a streptococcus hemolyticus septicemia after daily dosage with thyroid 180 mg. for 44 days. Two study infants had persistent systolic murmurs and one of these had developed the early signs of retrolental fibroplasia at the time of discharge. Another study infant contracted an upper respiratory infection after daily dosage with thyroid 120 mg. for 15 days; treatment was continued and he recovered. Two other infants developed severe upper respiratory infections after daily dosage, respectively, with thyroid 180 mg. for 18 days and thyroxin 0.2 mg. for 21 days; medications were stopped at body weights of 1940 and 2005 gm. and they recovered. One developed respirations of 60 to 80, a pulse rate of over 200 and tremors, after daily dosage for 18 days with thyroxin 0.2 mg.; medication was discontinued at 2025 gm. and the baby recovered. Another developed a pulse rate of 200 after daily dosage for 10 days with thyroid 180 mg. This infant was given the same treatment for 20 additional days; his pulse varied from 180 to 200 but he progressed satisfactorily and was apparently well on discharge.

G. Protein-bound Iodine Levels.

Table 6 shows average protein-bound iodine levels, in terms of μg./100 cc. serum, of all groups of infants before treatment and after successive weeks of treatment. These levels were measured as approximations of circulating thyroxin. It was not always possible to obtain adequate weekly blood samples from all of the infants under observation; figures in parentheses indicate the number of determinations on which each mean is based. Where this number is 3 or more, the standard error of the mean is given.

Numbers are too small for statistical analysis. It is evident, however, that daily dosage with thyroid 120 mg. is without apparent effect; a daily dose of thyroid 180 mg. or

TABLE 6

MEAN PROTEIN-BOUND IODINE ± S.E. (μg./100 cc. serum)

Type of Treatment	Before* Treatment	1 wk. Treatment	2 wk. Treatment	3 wk. Treatment	4 wk. Treatment	5 wk. Treatment	6 wk. Treatment	7 wk. Treatment
Control	5.0± .52 (18)	5.4± .58 (19)	5.1± .45 (14)	5.7± .56 (9)	5.0± .83 (5)	5.5± .99 (3)	—	—
Thyroid 120 mg./day	6.4± 1.5 (4)	4.3± .99 (3)	6.5± .95 (5)	6.9± .64 (3)	6.9 (1)	5.5 (1)	—	—
Thyroid 180 mg./day	5.7± .81 (4)	8.9± .49 (6)	6.8± .33 (6)	7.8± 1.1 (5)	7.5± 1.2 (3)	7.9 (2)	6.9± 1.1 (3)	6.1 (2)
Thyroxin 0.2 mg./day	7.2± 1.4 (6)	11.8± .93 (9)	10.9± .88 (9)	10.0± 1.4 (7)	9.1 (2)	11.4 (1)	—	—

* Mean value of 32 determinations in this column: 5.7± .47.

thyroxin 0.2 mg. appears to be necessary to raise the level of protein-bound iodine. The magnitude of the rise is greatest after the first week of medication and the thyroxin-treated infants show the highest levels. The two highest values which were determined, 15.3 and 16.2, were observed after 7 and 22 days, respectively, of treatment with thyroxin 0.2 mg.; both of these infants were clinically well at the time of these observations. There was no correlation between the serum protein-bound iodine levels of the control infants and their body weights, clinical condition or progress.

Discussion

Daily doses as large as thyroid 180 mg. or thyroxin 0.2 mg. for time periods averaging over three weeks had no effect upon the caloric and fluid intake, the gavage incidence, the amount of vomiting, the skin color or the body temperature of the study infants. Such dosage, however, decreased average daily weight gain significantly and the babies so treated showed an increased incidence of diarrhea and more rapid pulse rates. These data indicate that daily dosage with thyroid 120 mg. or less has no observable effect but daily dosage with thyroid 180 mg. or thyroxin 0.2 mg. may cause toxic symptoms in premature infants.

As previously noted, the initial red cell counts and hemoglobin levels of the study infants treated with thyroid 180 mg. or thyroxin 0.2 mg. were lower than those of the control infants. Thus, subsequent drops of similar magnitude in all groups resulted in lowest readings for these study babies. Anemia, however, does not entirely explain the increased use of blood transfusions in these groups. The impression remains that they were most often administered, as is generally the case in this clinic, because of unsatisfactory clinical condition and progress.

The mean protein-bound iodine level of 32 untreated infants was $5.7 \pm .47$ at an average age of 9 days. Mean values for the control infants did not differ significantly from this figure during a subsequent five week period. Although these levels are slightly lower than those reported for full term infants of similar postnatal ages,[6] they do not suggest that the premature infant is deficient in circulating thyroxin. It is pertinent to note here that many anatomic and chemical studies have indicated active function of the fetal thyroid gland.[7]

Daily dosage with thyroid 120 mg. produced no observable clinical effect nor did it raise the level of protein-bound iodine in the serum. Daily dosage with thyroid 180 mg., on the other hand, produced clinical effects and raised the iodine level. Euthyroid adults exhibit similar changes when from 0.18 to 0.36 gm. thyroid are given daily and smaller doses are without observable effect.[8] It has been shown, furthermore, that the thyroidal uptake of labelled radioactive iodine decreases markedly or ceases entirely in the presence of sufficient amounts of exogenous thyroid.[9] In children, the iodine uptake can be suppressed by daily doses of from 0.15 to 0.3 gm. thyroid.[10] These facts suggest that the normal thyroid gland adjusts to exogenous thyroid medication by a decreased production and release of thyroxin.[11] Homeostasis is lost only when thyroid is administered in amounts which exceed the normal output of the gland.

It is of interest that thyroid doses of like magnitude are necessary to produce therapeutic effects in premature infants and in euthyroid children and adults. This implies that the thyroid gland of the premature baby produces and releases thyroxin in amounts comparable to those of normal, older human beings, but does not exclude the possibility that the observed findings are related to altered transport, degradation or excretion of the

hormone. Since more than 120 mg. exogenous thyroid, given daily, are necessary to accomplish dosage-response relationships, it would seem that the gland of the premature infant has a usual 24 hour production approximating this amount. Medication of the athyrotic cretin should be adjusted with this in mind.

The effects of daily dosage with thyroxin 0.2 mg. were at least as great as those with thyroid 180 mg. This is in agreement with observations in older infants which show that the metabolic potency of thyroxin, in equi-iodine amounts, exceeds that of thyroid,[12] and with Salter's statement that the clinical effects of thyroxin 0.1 mg. appear to approximate those of 90 mg. thyroid.[13]

Moncrieff's observations of the benefits conferred upon premature infants from daily thyroid medication[2, 3] are not confirmed by this study. This is not surprising in view of the known activity of the fetal thyroid gland and of the hormonal production of the gland of the premature infant which seems to approximate that of the full term baby. If such production approaches thyroid 120 mg./day, a dose of 3.0 or 6.0 mg. thyroid extract/0.5 kg./day for a two week period could not be expected to give therapeutic effects. It should be added, however, that Moncrieff treated his babies in the earliest days of their lives when the risks of prematurity are most evident and he emphasized that it was difficult to see improvement when care is good and morbidity and mortality are low. The infants in the present series were selected and observed after the first week of life and they had already passed the age when the serum protein-bound iodine level of the full term infant is known to be elevated.[6] From the present study, it is not possible to conclude that thyroid medication is without benefit during the first few days of life of the premature infant. After the first week, however, such medication is not helpful and is sometimes harmful unless the infant is a congenital cretin.

Hunger or failure to gain weight usually determined the caloric intake of the 48 infants in this study. They ingested an average of approximately 150 calories/kg. body weight/24 hours and they accomplished an average gain in weight of more than 30 gm. per day, showing a "caloric intake considerably greater than that generally considered either necessary for optimum growth, or safe,"[14] and a daily weight increment larger than is usually achieved by premature infants. Their average weight gain agrees closely with that reported for two other groups of premature infants who were fed on a similar self-regulatory regimen.[14, 15] It may be explained in part by the fact that the babies in this series were in good health, more than one week of age and over 1500 gm. in weight when they were selected for observation. The unusually high caloric intake must, however, have been important and does not seem to have harmed the infants. The fetus gains an average of 21, 26 and 32 gm. per day during the 8th, 9th and 10th lunar months of gestation, respectively.[16] It seems reasonable to expect similar weight gains in healthy, premature infants of comparable ages. The present series shows that this is possible if the caloric intake is adequate.

Summary and Conclusions

Forty-eight premature infants, whose condition seemed satisfactory at one week of age and whose weights approximated 1500 gm., were selected for this study. Even-numbered infants in the series were given daily doses of desiccated thyroid or thyroxin for periods averaging 3½ weeks; odd-numbered infants were given placebos of lactose according to the same schedule. The clinical progress of the infants was noted and weekly red cell counts, hemoglobin and serum protein-bound iodine levels were determined.

1. Daily doses of 60 to 120 mg. thyroid produced no significant effects upon clinical condition and progress or upon the protein-bound iodine level.

2. Daily doses of thyroid 180 mg. or thyroxin 0.2 mg. did not affect the caloric and fluid intake, the gavage incidence, the amount of vomiting, the skin color or the body temperature. Such dosage, however, decreased the weight gain, increased the pulse rate and increased the incidence of diarrhea. A higher percentage of infants so treated required blood transfusions and did not fare so well clinically. The level of serum protein-bound iodine was elevated. The administration of thyroid or thyroxin to premature infants selected as noted above is therefore without observable benefit and is sometimes harmful. The effects of daily dosage with thyroxin 0.2 mg. were at least as great as those with thyroid 180 mg.

3. The mean protein-bound iodine level of 32 untreated infants was $5.7 \pm .47$ at an average age of 9 days, and mean values for the control infants did not differ significantly from this figure during a subsequent five week period. These levels do not suggest that the premature infant is deficient in circulating thyroxin.

4. Thyroid doses exceeding 120 mg./day are necessary to produce pharmacologic effects in premature infants and in euthyroid children and adults. This implies that the thyroid gland of the premature infant produces and releases thyroxin in amounts comparable to those of normal, older human beings and approximating 120 mg. thyroid/24 hours. Medication of the athyrotic cretin should be adjusted with this in mind.

5. When caloric intake is adjusted by the desires of the premature infant, he ingests an average of about 150 calories/kg. body weight/24 hours. On such a regimen, his weight gain approximates that of his fetal colleague of the same gestational age and averages more than 30 gm./day.

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SPANISH ABSTRACT

Efectos del Extracto Tiroideo o la Tiroxina en los Niños Prematuros

En 1938 Moncrieff observó que los prematuros se alimentaban mejor, controlaban su temperatura dentro de límites normales y presentaban menor mortalidad con la ingestión diaria de seis miligramos de extracto tiroideo por kilo de peso; desde esa fecha no se ha presentado otro trabajo en este sentido. El artículo aquí resumido señala los resultados observados con tiroxina administrada a 24 prematuros, que no confirman los efectos benéficos señalados por Moncrieff; los autores aclaran que de este estudio no se puede concluir tampoco que la medicación tiroidea no tenga efecto durante los primeros días de vida del niño prematuro; señalan, sin embargo, que tal medicación después de la primera semana no tiene ninguñ efecto favorable, y sí en ocasiones desfavorable, a menos que el prematuro sea un cretino congénito.

Este estudio se basa en la observación de 48 prematuros con buen estado general a la semana de edad y peso alrededor de 1,500 gramos. Se les dió tiroide desecado a 24 de ellos durante 3 semanas y media; los otros 24 niños sirvieron de control y recibieron sólo lactosa durante el mismo período. Los resultados observados fueron los siguientes:

1. El estado clínico y los niveles de yodo protéico no fueron alterados con dosis diarias de 6 a 12 centigramos de tiroides.

2. Con dosis diarias de 18 centigramos de tiroides ó con 0.2 miligramos de tiroxina no se vieron alteraciones en la ingestión calórica e hídrica, en el número o frecuencia de vómitos, en el color de la piel o temperatura corporal, aun cuando sí hubo disminución en la ganancia de peso, aumento en la frecuencia del pulso y de diarrea, así como ascenso en los niveles de yodo proteico; en cambio un alto porcentaje de estos niños necesitaron transfusiones sanguíneas y no mostraron progreso clínico.

3. La cifra promedio de yodo proteico en 32 niños no tratados fué de $5.7 \pm .47$ a una edad promedio de nueve días, valores que no difirieron significativamente en los niños control durante un período de 5 semanas.

4. Se requieren dosis de tiroides superiores a 12 centigramos por día para obtener efectos farmacológicos tanto en niños prematuros como en niños y adultos tiroido-normales. Según los autores esto significa que la tiroides del prematuro funciona con actividad semejante a la de los sujetos normales.

5. La ingestión calórica ajustada a los deseos del prematuro alcanza un promedio de 150 calorías por kilo de peso en 24 horas. Con un régimen de este tipo su ganancia en peso es semejante a la de un feto con la misma edad uterina y corresponde a un promedio de 30 gramos por día.

125 DeSoto Street

URINARY WATER EXCRETION AND NEUROHYPOPHYSIAL FUNCTION IN FULL TERM AND PREMATURE INFANTS SHORTLY AFTER BIRTH

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IN RECENT years the intravenous administration of fluids has been recognized as desirable in the therapy of an increasing number of conditions in infants. It seems important to describe some of the limitations of the ability of young or premature infants to handle the water that is introduced into their extracellular fluid in this manner.

The inability of the kidney of young infants to conserve water by the production of a concentrated urine has been reported.[1-3] Very little has been published concerning the capacity of the young infant to dilute his urine when excess fluid is present. Ohlmann[4] gave a group of infants up to one year of age 200 cc. water by mouth after an overnight fast. He found that the oldest did excrete this dose of water in five hours but that infants under 3 months of age excreted approximately half as much. Lasch,[5] giving a smaller dose of water to young infants, confirmed these findings. Recently Barnett and others[6] reported on the limitations of the response of premature infants to the administration of excess water and dehydration. Their results indicate that although the kidneys of premature infants do not function at an adult level, the difference is less than previously thought. Similar results have been observed in newborn animals. Adolph[7] working with puppies, Heller[8] and McCance[9] with rats and Dicker[10] with guinea pigs found that little if any diuresis followed the administration of 5% of the body weight of water given to newborn animals; the water was excreted slowly over a long period.

Of prime importance in the urinary excretion of water is the antidiuretic hormone of the neurohypophysis. Heller[11] attempted to explain some of the limitations of young infants' kidneys in terms of their inability to respond to antidiuretic hormone. He observed very little response to injections of large doses of antidiuretic hormone in young infants as compared with adults. His interpretation of these results are questioned since a diuresis was in progress in the adults but not in the infants when the hormone was administered. Barnett and his colleagues[12] reported the comparative responses of a 6 day old infant to a 16 hour thirst and to 1 milliunit (m.u.) of pitressin per minute infused in 0.9% saline for approximately 30 minutes. Since the increase in urine concentration was greater in response to the period of thirst than to the large dose of hormone, it was concluded that the infant's kidney had responded inadequately to the exogenous hormone. Many factors which influence the kidney's response to antidiuretic hormone were not constant in the two periods compared in this infant. It is therefore difficult to interpret these results.

The investigation here reported represents an attempt to describe further the factors that limit water excretion in young full term and premature infants.

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METHODS

All infants in this study were from the newborn nursery in Sloane Hospital or from the premature unit in Babies Hospital. The infants were examined before each study and were considered to be in good condition. The older children were patients in Babies Hospital who had recovered from minimal infections or minor surgical procedures. The adults were normal healthy volunteers.

Urine samples from infants were collected through an in-dwelling catheter directly into cylinders graduated to 0.05 cc. The bladder was emptied by applying pressure to the suprapubic region following the introduction of 1 to 3 cc. air.

Water was given orally through a small plastic tube which fits a No. 23 needle. The tube was inserted into the infant's nose and then passed into the stomach. It was allowed to remain in place 1 to 3 hr. before the start of an experiment.

The antidiuretic assays were carried out by the method reported by Ames, Moore and van Dyke.[13] Urine for assay was chilled and the pH adjusted to 4.0 until it was used. Assays were carried out within 12 hr. after collections were made. In every case in which antidiuretic activity of endogenous origin was present thioglycollate inactivation[14] was carried out in order to furnish further evidence for the identification of the antidiuretic substance as antidiuretic hormone.

The antidiuretic hormone used for injection was a special preparation of pitressin supplied by Parke, Davis and Co. which contained 80 pressor units and 3.8 oxytocic units/mg. powder.

Inulin clearances were carried out as described by Barnett et al.[12] Schreiner's[15] method was used for inulin determination. Creatinine was determined according to the Evelyn modification of the Folin-Wu method.

RESULTS

Excretion of Water by Full Term and Premature Infants

1. Oral Administration of water: The response of 67 infants to the oral administration of 30 cc. water/kg. body weight was observed. Urine samples were collected every 5 to 15 minutes for 3 hours and inulin or creatinine clearances were measured. The babies weighed between 1.2 and 5.7 kg. at the time the studies were carried out and they were from 3 hours to 92 days of age. Thirty-eight of them weighed between 0.8 and 2.0 kg. at birth. The graphic analysis of the data obtained is shown in chart 1.

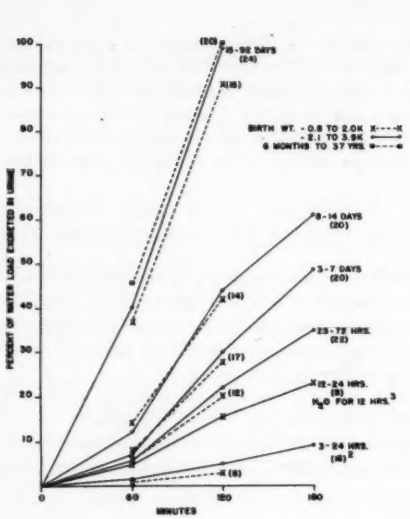
In the first 24 hours of life less than 10% of the water given is excreted in 3 hours. At 3 days of age about 35% of the water given was excreted in 3 hours and at 7 days of age 50% or more was excreted in the same period. In infants under 3 days of age the urine flow increased slightly and the minute volume remained a little higher than the control level throughout the experiment. After one week of age a diuresis of varying degree occurred at some time during the 3 hours. The infants studied were in a state of euhydration or appeared clinically to be in the overhydrated state commonly found in infants in the first days of life. The studies were carried out approximately one hour after a feeding.

TABLE 1

INFLUENCE OF AGE UPON ABILITY TO SECRETE DILUTE URINE FOLLOWING WATER LOAD

Age	No. of Observations	Specific Gravity of Urine	
		Before water load	60 min. after water
3–24 hr.	12	1.007±0.003*	1.006±0.004
1–3 days	18	1.006±0.005	1.004±0.005
4–7 days	15	1.008±0.002	1.003±0.003
>7 days	16	1.010±0.003	1.002±0.002

* Mean±standard error.



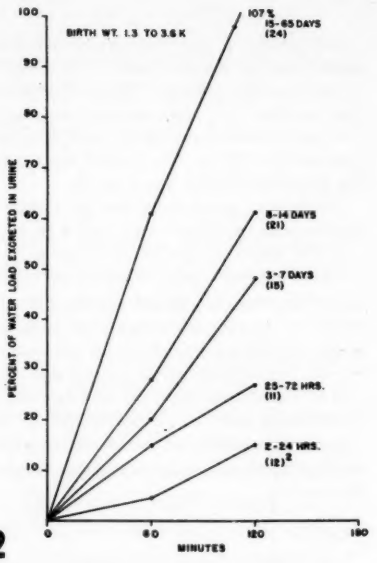


CHART 1. Comparison of water excretion in different age and weight groups following oral administration of water 30 cc./kg. body weight at —15 min.

[2] No. of patients in each group.

[3] This group received 15 cc. water every 3 hr. for 12 hr. prior to study.

CHART 2. Comparison of water excreted by various age groups following intravenous administration of 2.5% glucose as 30 cc./kg. body weight given at approximately —10 to 0 min.

[2] No. of patients in each group.

Eight infants less than 24 hours old were given 15 cc. water every 3 hours in the 12 hours prior to the administration of a water load. The total urine output in the 3 hours following the test load was greater than that excreted by 26 infants of the same age who received no added fluids before a similar water load. When a double dose of water was given at one time to six other infants of this same age the rate of urine flow did not increase appreciably. No true diuresis was observed in any of these infants.

Changes in the specific gravity of the urine excreted by the infants during the studies described above before and following a water load are summarized in table 1.

2. Intravenous Administration of Water (hypotonic glucose solution): A water load was induced in 42 infants by the intravenous administration of fluids. When water was given orally, the variables of the amount of water and the rate of its absorption by the stomach and intestines were present and a number of small infants had to be excluded from the study because they were unable to retain large doses of water. To avoid an osmotic diuresis caused by 5% glucose in water given intravenously a 2.5% solution was given in the experiments charted in chart 2. In this group of experiments 42 infants were studied, 18 of whom weighed less than 2.0 kg. at birth. Little diuresis followed the intravenous administration of fluids in infants under 24 hours old. The pattern of water excretion in the various age groups is similar to that observed after fluid had been given by mouth. The onset of diuresis when it occurred was approximately 15 to 20

minutes earlier following intravenous fluids but did not otherwise differ from that observed following oral fluids. The changes in specific gravity of the urine before and after water loads were given were similar in magnitude to those observed when water was given orally.

3. Water Excretion by Full Term and Premature Infants: In chart 1 the data obtained from premature infants under 2.0 kg. in weight at birth are charted separately from those derived from the larger premature and full term infants. It can be seen that immaturity apparently had little influence on the rate of development of this function. Although the comparative portions of the water load excreted in two hours are less at all ages, the difference between the means of the outputs of large and small infants is not significant ($P = 0.1$). Premature infants at 3 or 4 weeks of age can excrete water more efficiently than one week old full term infants even when the premature babies weigh considerably less and appear more immature in many other respects.

4. Water Excretion in Relation to Age: Ten infants whose birth weights were between 1.9 and 2.6 kg. were studied extensively over a 30 day period. Their response to 30 cc. of 2.5% glucose intravenously/kg. body weight was measured every few days. Average values from these data are summarized in chart 3. These data serve to demonstrate the relative ability to diurese at different ages. The volumes of urine excreted/minute as well as the inulin clearances are shown following glucose infusions. Very little if any diuresis can be said to occur under 3 days of age. At one month of age all the infants studied responded to the injection or ingestion of water with a definite rise in urine flow, over 85% of the water given being excreted at the end of 2 hours. The most rapid develop-

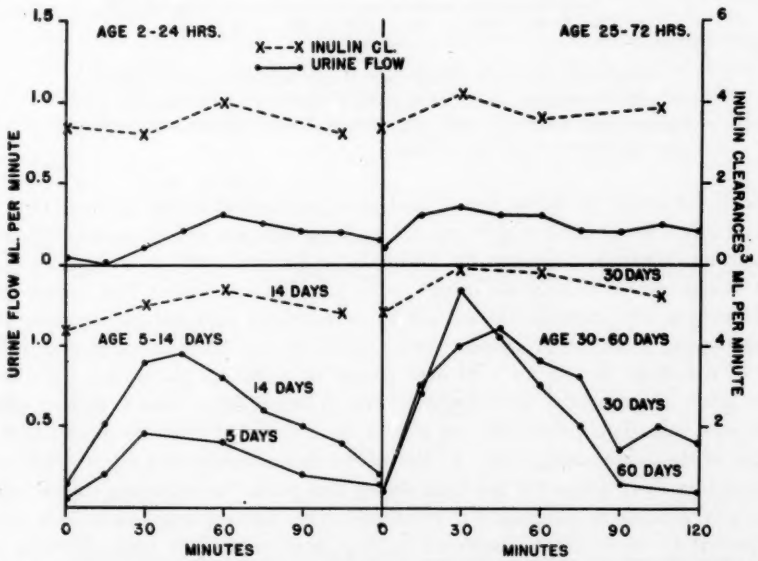


CHART 3. Mean response of 10 infants during first month of life to 2.5% glucose as 30 cc./kg. body weight given at approximately —10 to 0 min. Each curve represents average values from 10 infants who were studied repeatedly over 30 day period. Birth weights were between 1.9 and 2.6 kg. Curve for 60 days was drawn from data obtained from 10 similar infants.

[3] Absolute values for inulin clearances.

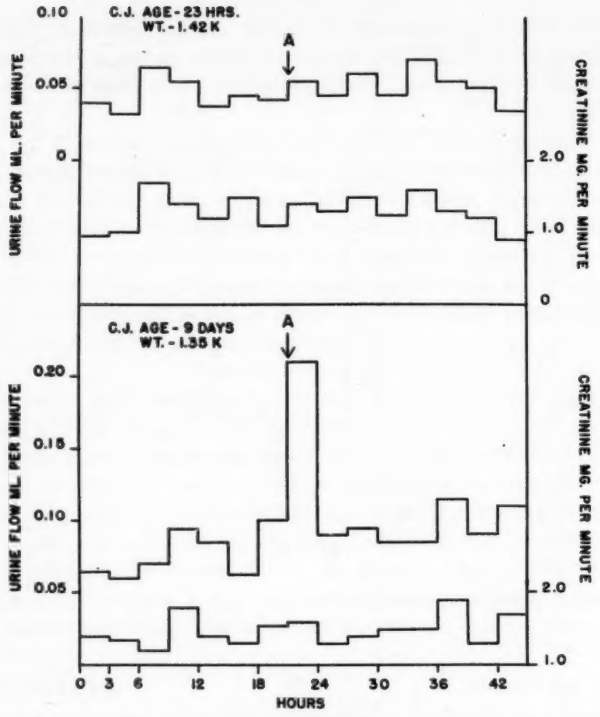


CHART 4. Urine flow (upper curve) and creatinine excretion (lower curve) of premature infant tested at 23 hr. and at 9 days of age. At A 30 cc./kg. body weight of 2.5% glucose solution was injected intravenously during interval of less than 10 min.

ment of the ability to excrete a fluid load in a short period of time occurred in a premature infant whose birth weight was 1.2 kg. This baby was able to excrete 50% of an infused water load in 2 hours by the fourth day of life and 100% at the age of 12 days.

It was of interest to study the infants under 3 days of age further. Five infants whose birth weights were between 1.4 and 2.0 kg. were placed on a metabolism frame in an incubator and 3 hour urine samples were collected for 24 hours on the second or third day of life. Near the end of a 24 hour period 30 cc. of 2.5 glucose/kg. body weight were given intravenously. Urine samples were collected for a second 24 hour period. This same procedure was carried out at 8 to 10 days of age when the fluid intake and output of the infant were greater. A chart of the data obtained from one of these babies is shown in chart 4. Since it has been shown that painful or excitatory stimuli cause a release of antidiuretic hormone,[16–18] precautions were taken to avoid exciting or causing discomfort to these infants. Inasmuch as they were small, only loose restraints were necessary which did not appear to cause much discomfort. They were given their regular formulae every three hours. Their only painful experience was the injection of the glucose solution and this was over in 5 to 10 minutes. Endogenous creatinine excretion was the only measurement of kidney function carried out. In those less than 3 days of age no significant diuresis was observed in any 3 hour period and there was merely an

increase in the total 24 hour urine specimen following fluid administration. On the other hand, at 8 to 10 days of age an increase in urine flow was observed in the same babies in the 3 hour period immediately following the glucose infusion.

It has been shown that in normal individuals endogenous creatinine clearances are very close to inulin clearances and probably measure glomerular filtration rates.[19] A rise in creatinine clearance of between 5 and 12% was observed following fluid administration orally or intravenously in 26 of 37 infants studied under 3 days of age. In infants over 10 days of age the rise in creatinine clearance following a water load varied between 14 and 32% in 55 of 67 infants studied. No appreciable change in clearance rates was seen in 23 (22%) in a group of 104 infants at all ages. Changes in inulin clearances were of a magnitude similar to those observed with creatinine clearances in 16 infants.

Response to Exogenous Antidiuretic Hormone

It has been well substantiated that the antidiuretic effect of the neurohypophysial hormone can be demonstrated only when a water diuresis is in progress. Since a diuresis was not induced in infants in the first 3 days of life, attempts to demonstrate a response to the antidiuretic hormone should be unsuccessful. In the first weeks of life the response should be variable. This proved to be true. Studies were carried out in a manner similar to those described above. Fifty cubic centimeters of 2.5% glucose/kg. body weight were given intravenously to 20 infants under 3 days of age. No diuresis ensued and pitressin 0.5 to 5.0 m.u. given intravenously between 20 and 40 minutes after the fluid administration had little or no effect on the urinary output. When more than 1.0 m.u. pitressin was given there was transitory blanching of the skin, restlessness, flatus and the expulsion of feces with moderate force.

In infants over 3 days of age pitressin 0.5 m.u. injected intravenously always stopped a diuresis. The length of the period of low urine flow depended on the degree of diuresis in effect at the time the hormone was given and the amount of discomfort the infant suffered during and following its administration. For several reasons it is difficult

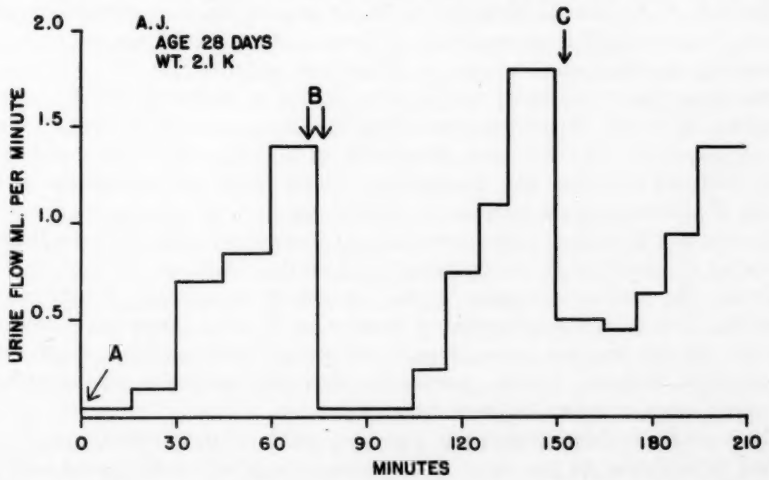


Chart 5. Urine flow of 28 day old infant after water, discomfort and pitressin. A. 65 cc. water given at −30 min.; B. passage of gavage tube and 30 cc. water by mouth; C. 0.5 m.u. pitressin intravenously.

to assess the response to the hormone quantitatively and to compare the antidiuretic effect in the various age groups. Even in animals with diabetes insipidus the response to known amounts of ADH varies for the most part with the state of hydration of the animal and the solute load in the urine. In animals and humans with intact neurohypophyses there is always the possibility of the release of endogenous hormone caused by excitation or discomfort.[16–18] When a procedure caused discomfort there frequently was a fall in urine flow. Chart 5 demonstrates such a response to the passage of a No. 10 French catheter through an infant's mouth. Thirty minutes prior to this, 65 cc. H_2O had been passed through a small plastic tube which had been in place in the infant's nose. Urine collected during this period of antidiuretic effect was found to have antidiuretic activity equivalent to pitressin 0.75 m.u./cc. urine. The response to 0.5 m.u. pitressin is also summarized in this figure. The pitressin was added to an infusion which had been running into a wrist vein, and the infant slept throughout the entire procedure.

In spite of the variability of the responses to the hormone it can be said that when a diuresis was established an antidiuretic response was obtained in all infants over 3 days of age following either a painful stimulus or the administration of antidiuretic hormone. When pitressin 0.5 m.u. was given to 42 infants over 5 days of age, urine flow fell to less than 0.25 cc./minute as compared with an average flow before hormone administration of 2.8 cc./minute. The period of antidiuresis varied according to the amount of excitement which accompanied the injection. In 12 infants to whom a continuous infusion of 2.5% glucose was being administered and who could be given the hormone without the discomfort of an additional injection, the period of antidiuresis was over in 30 to 40 minutes. The difficulty of avoiding psychic effects was greater in the older infants and children for whom restraints were necessary for any injection or infusion. Transient and apparently spontaneous falls in urine flow were even more frequent in the older children. As far as comparison was possible between infants and older children the response to exogenous hormone (0.5 to 2.5 m.u.) could not be said to be different.

Secretion of Antidiuretic Hormone in Young Infants: Since no response to antidiuretic hormone could be demonstrated in infants under 3 days of age, evidence of a functioning neurohypophysis was sought. Fluids were withheld from 23 infants under 3 days of age for 6 to 8 hours. Urines were collected in the last 30 minutes without disturbing the infant. These urines were found to contain an antidiuretic activity which was equivalent to 1.25 ± 0.25 m.u. pitressin/cc. urine. This activity was abolished by alkali, heat and reduction with thioglycollate,[14] effects which are characteristic of the activity of neurohypophysial hormone. Six children aged 2 to 12 years had no detectable antidiuretic activity in their urine after 6 hours of thirst. Eight adults who were thirsted 12 hours had inactive urines, but following a 24 hour thirst there was 0.25 m.u./cc. in 2 specimens. The presence of hormone in the urines of the young babies probably means either that there is excessive liberation of hormone, or decreased destruction or inactivation, or that the hormone passes through the infant's glomeruli more readily than through adult glomeruli. It is also possible that the young infant loses more water/kg./minute and therefore is more depleted after a 6 hour thirst.

There are no available observations suggesting which of these factors is most important. Nevertheless, the presence of the hormone in the infant's urine is good evidence of a functioning neurohypophysis.

Discussion

It is apparent from the results obtained in these studies that the ability of the newborn infant to excrete a water load develops gradually in the first month of life. In the first 3 days of life it is difficult to be certain that the large doses of fluid administered in the course of these observations were associated with any change in renal function. These young infants are apparently unable to respond with a diuresis after an increase in body water. The rate of development of the ability to excrete a water load is little influenced by the maturity of the infant at birth as judged by body weight and period of gestation.

The cause of the early inability to excrete large doses of fluids is not clear from the evidence at hand. Three organs are chiefly involved in the urinary excretion of water; the kidney, the adrenals, and the neurohypophysis. We know that the kidney of the young infant is immature at birth. It has been shown by others that the glomerular filtration rates of premature and full term infants are half those of adults when compared on the basis of surface area.[12, 20–23] The adult levels are not reached until the end of the first year or, according to others, by the end of the second year. Tubular function in young infants as measured by diodrast® and p-amino-hippuric acid clearances has also been found to be lower than in adults. Adult levels of tubular function are not reached until the end of the first year. The relatively low level of both glomerular and tubular functions at birth accounts in part for the early inability to excrete large doses of water. Yet some other deficiency must play a far more important role, since the infant is able to excrete a water load in a mature manner as early as at the age of one month rather than at 1 or 2 years.

It has been shown that patients with adrenal cortical insufficiency do not respond to water loads in the usual manner. No sudden diuresis ensues following the administration of a large dose of fluid but there is a gradual excretion of the excess water over a long period of time. This resembles the performance observed in young infants under 3 days of age. Our knowledge of the capacity of the adrenals in newborn infants to respond to stress of any kind is meager. Jailer[24] found that the adrenals of newborn rats did respond to ACTH but that there was no evidence of ACTH release from the pituitary after stress. Venning et al.[25] demonstrated an increased excretion of glucocorticoids in newborn human infants following trauma. This has been interpreted to mean that the anterior pituitary does respond to stress and in turn stimulates the adrenals in the human infant. How soon the adrenal cortex is able to function at an adult level is not known. However at present we have no evidence to support the hypothesis that adrenal hypofunction can account for the inability of the young infant to excrete a water load rapidly.

The neurohypophysis is of the utmost importance in the conservation of water. During water diuresis the release of ADH is suppressed. When diuresis occurs, exogenous as well as endogenous antidiuretic hormone, released in response to discomfort or excitation, can produce an antidiuretic effect in older infants and adults. Whether the effect is less in infants remains a question since it is difficult to evaluate quantitatively a response to a known dose of hormone in the presence of an intact neurohypophysis. Antidiuretic activity was present in the urines of young infants after thirsting. Since the substance responsible for this activity had several of the characteristics of pituitary ADH, we assume that the neurohypophysis is functioning in this group at an early age. In the absence of a functioning neurohypophysis in the adult, diuresis in response to an increased water load is not impaired and the kidneys respond to exogenous antidiuretic hormone. The very young

infant is unable to vary his urine flow to any great extent when his fluid intake changes, and no response to exogenous antidiuretic hormone can be demonstrated. Therefore, the immature responses of the very young infant do not imply neurohypophysial dysfunction. By exclusion, the low level of kidney function and a possible adrenal insufficiency remain as probable factors accounting for the deficient excretion of water in the first weeks of life.

It is perhaps not unexpected that additional hydration facilitates the excretion of water even in the very young infant. This was demonstrated in the 8 infants under 24 hours old who were given 60 cc. water in 12 hours prior to a large dose of water. Their ability to excrete the water load was much greater than that of infants of the same age receiving only the single large dose of water, although no real diuresis was observed in any of these infants under 3 days of age.

Summary

In infants studied in the first month of life there was a gradual development of the ability to excrete excess water in a short period of time. When a water load was given according to body weight, orally or intravenously, no diuresis was observed in infants under 3 days of age. In comparison, all individuals tested over 3 days of age responded with a definite increase in water excretion. As early as 2 weeks of age and in all infants over one month of age the entire water load of 3 to 5% of their body weight was excreted in a three hour period following the administration of fluid. No difference in the diuretic response to a water load was apparent in full term and premature infants of comparable postpartum age.

Antidiuretic hormone whether produced endogenously following thirst, excitation or pain, or injected in the form of exogenous antidiuretic principle, caused a decrease in urine output only in infants who received a water load and who were responding to it with a diuresis.

When diuresis followed a water load, the degree of the renal response to antidiuretic hormone could not be compared in the various age groups studied, because of the inability to control a sudden release of endogenous hormone provoked by excitatory stimuli.

The hormone was detectable in the urines of infants under 3 days of age after fluid deprivation; this is assumed to be evidence of a functioning neurohypophysis.

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SPANISH ABSTRACT

La Excreción Urinaria de Agua y la Función Neurohipofisiaria en Niños a Término y Prematuros

El uso de la vía venosa para la introducción de soluciones a lactantes con diversos padecimientos a fin de realizar una terapéutica mejor y más rápida, ha dado interés al estudio de las limitaciones que lactantes a término y prematuros puedan tener para regular el agua agregada por dicha vía al contenido líquido extracelular. Este trabajo tiende a analizar algunos factores que limitan la excreción acuosa en estos seres. Los niños aquí estudiados fueron considerados normales; se les proporcionó agua por vía oral y por vía intravenosa (para ésta se empleó solución glucosada hipotónica); la orina se recolectó por cateterización; la acción antidiurética se analizó con el método de Ames, More y Van Dyke; la hormona antidiurética de origen exógeno fué una preparación especial de pitresin de Parke Davis y Co.; por último las pruebas de la inulina se realizaron de acuerdo con el método de Barnet y colaboradores, la determinación de inulina por de Schreiner y la creatinina por el de Evelin modificando el de Folin-Wu.

Los estudios realizados por estos autores sugieren que la capacidad de los recién nacidos para eliminar una sobrecarga hídrica se desarrolla gradualmente en el primer mes de edad y que en los primeros tres días de la vida, no se puede achacar la escasa eliminación exclusivamente a una alteración de la función renal. La madurez del niño al nacer, juzgada por su peso y por duración de su vida intrauterina, tampoco parece influir sobre el desarrollo de la capacidad excretora.

La causa de la incapacidad a esta edad no es clara; los tres órganos que intervienen en la excreción urinaria son el riñón, las suprarrenales y la neurohipófisis. La inmadurez del riñón, aceptada para los dos primeros años de vida, no impide que al mes el niño elimine el exceso de agua; entonces, se supone que haya alguna otra deficiencia que intervenga en la defectuosa eliminación de los primeros tres días de edad. La insuficiencia suprarrenal se considera como un factor al

respecto en los adultos; pero poco sabemos de la función de las adrenales en el recién nacido y por lo tanto no podemos sostener la hipótesis de que la hipofunción de esta glándula sea la responsable de la incapacidad del lactante para eliminar los excesos acuosos. Asímismo se conoce la importancia de la neurohipofísis en la conservación del agua; tanto en niños mayores como en adultos hay supresión de la hormona antidiurética durante la diuresis de agua, y viceversa, pero no se sabe si lo mismo sucede en lactantes.

Los autores concluyen que existe un desarrollo gradual de la capacidad excretora de agua durante el primer mes de la vida. En los tres primeros días, no se observa diuresis con un exceso de agua de acuerdo con el peso del niño, empleando bien la vía oral o la intravenosa; después de estos tres días de edad hay aumento definido en la excreción acuosa; desde las dos semanas de edad y en todos los niños después del mes de edad, la sobrecarga acuosa que alcance del 3 al 5% del perso corporal, se excreta en las tres horas siguientes a la administración del líquido, sin que se observe diferencia de la respuesta diurética entre niños a término y prematuros de edad semejante después del nacimiento.

La hormona antidiurética, tanto de producción endógena por sed, excitación o dolor, como inyectada, produjo un descenso en la excreción urinaria sólo en aquellos niños que recibieron la sobrecarga acuosa y estaban respondiendo con diuresis. Cuando se presentó la diuresis por la sobrecarga acuosa no se pudo comparar la respuesta renal a la hormona antidiurética en los diferentes grupos de edades estudiados, por la imposibilidad de controlar las descargas bruscas de hormona endógena provocada por las excitaciones. La hormona logró aislarse en la orina de niños menores de tres díase de edad tras un ayuno de agua; su presencia se acepta como prueba de actividad de la neurohipófisis.

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CONGENITAL LUNG CYSTS IN INFANTS

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RAPIDLY expanding congenital cysts of the lung may appear suddenly during infancy. Recognition is simple and prompt surgical treatment is effective. The condition is not common enough to be at one's diagnostic fingertips but is usually so characteristic and dramatic that one case leaves a lasting impression. Six congenital lung cysts, all emergencies, and all in infants, were seen within two years and form the basis of this report.

There are also symptomless congenital lung cysts of relatively small size which come to light when, for some reason or other, a roentgenogram of the chest is made. Advice concerning removal of such cysts is slanted by the past experience of the attending staff. Cysts, also called pneumatoceles or loculated emphysema, which develop as a sequel to staphlococcic pneumonia are the most common cause of radiolucent shadows in the lungs of infants. These cysts and small congenital cysts are those for which Caffey[1] in a recent report advises conservative treatment. Advice concerning such cysts obviously will be based on many considerations not pertinent to this discussion.

Interest is focused here only on the congenital lung cysts which are large enough to cause severe symptoms and demand prompt treatment. Acquired lung cysts following staphylococcic pneumonia during infancy may become emergencies because of size or rupture, but are not included in this review.

SYMPTOMS AND DIAGNOSIS

Cough, anorexia and moderately rapid breathing may be noted as early symptoms but are not impressive. Only when over a period of days, or more often hours, severe dyspnea and cyanosis are noted may the diagnosis be suspected. Physical examination of such a child in respiratory distress is, of course, in order but not too satisfactory. One will find diminished breath sounds and hyperresonance on the affected side with the mediastinal structures pushed over to the opposite side. If the child is in real respiratory distress, more will be accomplished by placing it in oxygen and immediately preparing for roentgenographic examination, than by going through the labor of an academically satisfactory physical examination.

Presumably the distressed infant will be seen in the nursery. The child should be placed in a covered crib or isolette, with a high concentration of oxygen, and should be sent to the x-ray department. If such conveniences are not at hand, the child may be transported in a buggy or on a cart while giving oxygen from a portable tank with a funnel placed over the child's face. Bedside RGs of an infant breathing 60 to 75 times a minute are often nothing more than a mass of misleading fuzzy shadows. With all in readiness, the infant can be taken out of the oxygen safely for the few moments required for making the RGs with a fast machine. The infant should be kept in the upright position with the hands above the head while the antero-posterior and lateral views are made. The infant

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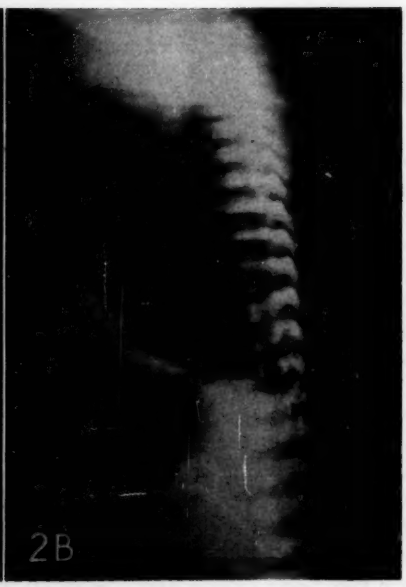
FIG. 1. Case 1, R.K. Admission P-A RG showing marked mediastinal shift to left due to cysts in right lung.

FIG. 2A and B. Case 2, J.H. Preoperative P-A and lateral RGs showing location of cysts in right lung. Note marked mediastinal displacement to left.



is quickly replaced in oxygen but is kept in the department until the films have been developed and proven satisfactory. This rather detailed review of the simple procedure of making a roentgenographic study of a dyspnoeic infant is justified only because good RGs are essential for the diagnosis and differentiation of translucent shadows in the chest of the newborn infant. Five possible diagnoses must be considered as the RGs are studied: congenital lung cysts, congenital diaphragmatic hernia, pneumatoceles secondary to staphylococcic pneumonia, tension pneumothorax and congenital lobar emphysema. The outstanding symptoms—dyspnea and cyanosis—are the same in each condition.

Congenital lung cysts, fortunately, are confined usually to one lobe or a portion of one lobe. They may be single but usually are loculated. The RG shows the clear air spaces (Figs. 1 and 2) divided by septa into large segments. Mediastinal structures are pushed to the opposite side and the adjacent lobe or lobes are collapsed and usually visible as triangular shadows.

A congenital diaphragmatic hernia on the left side is usually recognizable in a newborn child by the characteristic appearance of loops of bowel in the left hemithorax and by the displacement of the mediastinal structures to the right. However, if the diaphragmatic defect is on the right side and only a few loops of distended bowel are in the chest, it may be difficult to make a definitive diagnosis without giving the infant some contrast media by mouth and watching its progress through the bowel.

Pneumatoceles usually do not present a diagnostic problem if evidences of the etiologic pneumonia are still present. The history of fever, the clinical and roentgenographic findings of co-existing pneumonia practically always clinch the diagnosis of pneumatoceles. Aspiration of fluid from the chest and recovery of staphylococci confirm the diagnosis of pneumatoceles following pneumonia.[2] It is possible to mistake pneumatoceles for diaphragmatic hernia.

Tension pneumothorax may be spontaneous in the newborn infant or may be the result of a ruptured pneumatocele. In the former condition, half the chest is filled with air and the collapsed lung as an oval shadow is visible at the hilus. In the latter condition the lung may be only partially collapsed and will most likely still show signs of pneumonia. Free air will be seen in the chest and usually an unruptured cyst or cysts will be seen in the uncollapsed portion of the lung.

Congenital lobar emphysema is a relatively infrequent condition which has not often been described.[3] One lobe of the lung, generally the upper lobe on either side, is greatly distended, pushing the mediastinal structure to the opposite side and collapsing the uninvolved lower lobe. It is very difficult and sometimes impossible to differentiate this condition from a lung cyst. The only clue is the finer lung markings in the former condition. If an attempt is made to relieve the cyanotic infant by aspiration and no air can be withdrawn one promptly becomes suspicious that one is dealing with an emphysematous lung rather than a lung cyst.

Two illustrative cases are briefly outlined:

Case 1, R.K.: A 5 day old male infant was admitted to the hospital by ambulance with a history of rapid respiration and cyanosis of 24 hr.' duration. His birth had been at full term, breathing spontaneous and normal. On the fourth day of life cyanosis was seen after a feeding. Chest RGs revealed large cysts in the right lung (Fig. 1). It was impossible to be sure which lobe or lobes were involved.

The infant was afebrile and slightly cyanotic. Respiration rate was 60/min. Right hemithorax was hyperresonant and breath sounds were absent. Heart tones were heard far to the left of normal

position. Gas patterns throughout the bowel could be seen in the roentgen films and a rectal examination was negative.

Because dyspnea and cyanosis increased during a few hours of observation, surgery under intratracheal anaesthesia was performed as an emergency the day of admission. Chest was opened through the right 5th interspace and the right lower lobe containing a number of cysts was resected. Upper and middle lobes, completely collapsed, each about the size of a pecan nut, could be partially expanded by pressure on the anaesthetic bag. Chest was drained and closed snugly in layers. When the child had been returned to its crib, the end of the drainage tube was placed under water in a bottle to form a seal.

Pathologic examination confirmed the diagnosis of lung cyst.

Convalescence was uneventful and the child was discharged 2 wk. after operation, at which time the right middle and upper lobes had expanded sufficiently to fill the right thorax.

Case 2, J.H.: A 1 mo. old male infant was admitted by ambulance to the hospital with severe dyspnea and marked cyanosis. Fortunately, roentgen films taken at another hospital and accompanying the child were diagnostic of a lung cyst (Fig. 2). The baby was given emergency oxygen in the admitting room and the chest was quickly aspirated. The infant improved promptly.

A history was then obtained. This vigorous, apparently normal 4.1 kg. infant had been delivered spontaneously. The child was taken home and continued healthy until 2½ wk. of age, when it had an attack of dyspnea and vomiting. A change of formula stopped the vomiting. Dyspnea continued and cyanosis appeared. The infant was returned to the hospital where it had been born and roentgenographic studies of the chest were made. On 2 occasions the chest was aspirated and each time the infant was improved for a few days. Rather suddenly the symptoms became severe and the patient was transferred for emergency treatment.

After the chest had been aspirated in the admitting room, preparations were made for immediate surgery. A 20 cc. syringe and needle were kept at the baby's side and a resident remained in constant attendance.

The anaesthesiologist, Dr. William O. McQuiston, intubated the infant but could not obtain even first plane anaesthesia because the exchange of gases was so inadequate. The chest was aspirated again but cyanosis persisted. It was obvious that immediate relief was necessary. The skin of the right chest was hastily prepared and without towels, drapes or gowns, and with no attention to hemostasis the right chest was opened. The tense cyst in the right upper lobe herniated out between the ribs separated by finger traction. Immediately the heart, which had practically stopped, began to beat normally, the cyanosis disappeared, the child could now be anaesthesized and the operation could be continued in an orderly fashion. It was found that the cystic disease was confined to the anterior apical segment of the right upper lobe. This segment was resected. The chest was drained, closed, and the infant treated as reported in Case 1. The pathologist confirmed the diagnosis of lung cyst.

Convalescence was uneventful and the child was discharged from the hospital on the eleventh day following surgery.

Treatment

This paper is not concerned with the nonemergency type of lung cyst which can be studied leisurely and treated as circumstances warrant. Too little attention has been given the infant who, because of an expanding lung cyst, becomes visibly cyanotic and distressingly dyspnoeic. In fact, it is only 12 years since Fischer et al.[4] reported the first successful emergency resection of a lung cyst in a one month old baby.

So soon as a definitive diagnosis of an expanding lung cyst has been made and confirmed by roentgenographic examination, the infant is literally followed by a physician with a large syringe and needle in his hands while preparations are being made for surgery. Aspiration of air from the cyst should be done only to relieve increasing dyspnea and deepening cyanosis; it is never done as an elective procedure. If aspiration has become necessary to relieve symptoms, the child from then on must be watched still more carefully because a pneumothorax may have resulted from puncturing the cyst. One may

be sure the cyst will promptly refill with air. Attaching continuous suction to a needle in the chest leads only to trouble. If the child for some reason must be transported to another institution it is probably safest to keep the child in oxygen and be ready to aspirate the chest as often as necessary until surgery can be done. (See Case 2.)

Surgical treatment presents no difficulties if an anaesthesiologist is available who can gently and surely intubate the infant and maintain a proper exchange of gases.

The chest is opened through a properly placed intercostal incision and the greatly expanded cyst is allowed to herniate itself out of the wound. So soon as the cyst has extruded itself from the chest, the infant will breathe better and the surgeon can unhurriedly proceed with resection of a segment or a lobe of lung, as circumstances demand. After resection is completed, the chest is drained with a catheter which is attached to a water seal bottle after the infant is returned to its crib.

Postoperative care consists merely of keeping the infant in oxygen for 24 hours, more or less, giving the proper amount of antibiotics and providing adequate humidification if there is any sign of postanaesthetic laryngotracheitis.

SUMMARY

The diagnosis and treatment of congenital lung cysts producing severe symptoms are discussed. The cases of six infants form the basis of this report. All had such severe dyspnea and cyanosis that emergency operations were necessary. All six infants made uneventful recoveries. The youngest child was five days old.

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SPANISH ABSTRACT

Quistes Congénitos del Pulmón en la Infancia

Aun cuando los quistes congénitos del pulmón no son tan frecuentes como para pensar en ellos a cada momento, en ocasiones presentan síntomas tan severos y dramáticos que los casos se convierten en problemas de emergencia. En este artículo se estudian seis casos que requirieron tratamiento inmediato quirúrgico. Los síntomas iniciales son tos, anorexia y polipnea, seguidas en unas cuantas horas o días de disnea intensa y cianosis; clínicamente se pueden confundir con hernia diafragmática congénita, neumatocele secundario a neumonía estafilocóccica, neumotórax a presión y enfisema lobar congénito, pues los signos más notables (disnea y cianosis) son los mismos en todos ellos; el diagnóstico diferencial se hace por medio de los rayos X. El tratamiento es fundamentalmente quirúrgico al presentarse la emergencia: aspiración de aire de los quistes para aliviar al niño de la disnea y la cianosis, e inmediatamente después toracotomía con resección segmentaria o lobar del pulmón, según las circunstancias. El post operatorio consiste en la administración de oxígeno, antibióticos y vapor.

Los seis casos presentados se recuperaron favorablemente. El más pequeño tenía cinco días de nacido.

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RADIOIODINE UPTAKE IN THE STUDY OF DIFFERENT TYPES OF HYPOTHYROIDISM IN CHILDHOOD

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THE application of radioiodine tracer technics to the clinical study of thyroid disorders depends upon measurements of radioactivity over the thyroid gland, in the urine and in the blood. Various workers have attempted to determine: (1) the total amount of the administered I^{131} which has been trapped by the thyroid gland at the end of 24 hours or longer, or the rate of its accumulation by the gland;[1-10] and (2) the rate of conversion of inorganic iodine into thyroid hormone as measured by (a) the discharge of I^{131} from the gland after the administration of KSCN or KI[11-14] or (b) the ratio of protein-bound I^{131} to the total I^{131} of the plasma.[15-19] Most workers have attempted to express the uptake by the thyroid gland in terms of the percentage of the dose of I^{131} administered, although technical difficulties frequently lead to considerable inaccuracy. The usefulness of the different methods depends upon the particular problem to be studied.

A number of workers have applied radioiodine tracer technics to study the effects of thyrotropic hormone upon thyroid function. Stanley and Astwood[20] showed that in euthyroid patients, when the ability of the thyroid gland to take up iodine had been suppressed by thyroid medication, the capacity for I^{131} uptake could be restored by the administration of thyrotropic hormone (TSH). Querido and Stanbury,[21] Werner et al.[7] and Levy et al.[22] measured the effect of TSH on the uptake of I^{131} in attempting to differentiate primary hypothyroidism from thyroid deficiency secondary to hypopituitarism.

Relatively few studies with radioiodine have been reported in children with hypothyroidism[2, 3, 8, 13, 14] and there has been little attempt to correlate the findings with the clinical symptomatology or the degree of thyroid deficiency. The pioneer work of Hamilton et al.[2] showed that in most cretins there was little or no uptake of I^{131} but that some "goitrous cretins" took up and retained large amounts of I^{131} in the enlarged glands. Stanbury and Hedges[13, 14] showed that the administration of KSCN to a number of patients with sporadic cretinism who had large nodular goiters caused a rapid release of previously accumulated I^{131} from the glands indicating that there was a disability in the conversion of inorganic iodine into organic compounds. In the nongoitrous forms of hypothyroidism various workers have confirmed the finding of a low or absent uptake of I^{131}. However, it has been shown[6, 7] that the uptake of I^{131} in hypothyroid patients varies from 1% to 15% of the administered dose, whereas 2% of supposedly euthyroid subjects take up less than 10%.

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The present studies were undertaken in the hope that they might offer some explanation for the marked variations observed in the symptomatology of hypothyroid children, and perhaps shed light on differences in etiology. The clinical differences between congenital cretins and children with acquired hypothyroidism depend to a large extent upon the level of development which the patient has attained before the thyroid deficiency begins. However, one frequently observes marked differences in the clinical picture of untreated hypothyroid patients 2 or 3 years of age whose osseous development had advanced little if at all above the birth level, indicating that the deficiency has existed since birth. In such cases, it is often impossible to demonstrate differences in the degree of thyroid deficiency by the usual studies of circulatory changes, serum cholesterol, B.M.R. or even protein-bound iodine. It was realized that the study of I^{131} uptake sheds no light on the functional ability of the thyroid gland to secrete hormone. It seemed, however, that such a study might demonstrate the presence or absence of small amounts of thyroid tissue and that the existence of such tissue might be correlated with the relatively milder types of clinical symptoms. It was possible also that cases might be found in which thyroid deficiency was due to inability of the gland to synthesize hormone rather than to absence of the gland.

Methods

Since it was anticipated that there would be slight, if any, uptake of I^{131} by most of the patients studied, it seemed impractical in view of the present inaccuracies of methods to attempt to calculate the radioactivity taken up by the gland as the percentage of the administered dose. It was considered that the demonstration of even small amounts of radioactivity persisting in the thyroid region for some days after all evidence of radioactivity had disappeared elsewhere in the body could be considered presumptive evidence of the presence of thyroid tissue. Accordingly all radioactivity was recorded in terms of counts/sec. Although the dose of I^{131}/kg. body weight was approximately the same in most patients, a comparison of counts/sec. retained in different patients gives only a crude relative measurement of the I^{131} accumulation.

I^{131} without carrier was injected intravenously into a vein of the arm or leg to avoid contamination of the skin of the neck which might occur if the infants were given the iodine orally and to obviate differences in gastrointestinal absorption. The dose was generally 1 microcurie/kg. body weight, although in some of the earlier cases 1.75 microcuries/kg. were given. Counts were made with a Victoreen Geiger Muller tube having an end window covered with mica and were recorded on a Tracerlab Autoscaler. A radiolead standard was used to check the constancy of the counter. The counter was centered over the neck just above the episternal notch and held in close proximity to but not touching the skin. To obtain the background of I^{131} in the general circulation, counts were taken similarly with the tube placed over the anterior thigh a short distance above the knee at a point where the circumference was approximately that of the neck. Counts were taken immediately after injection of I^{131} and at intervals of 10 to 15 min. during the 1st hr. They were then repeated hourly until the 4th to 6th hr. and again at 24 hr. Thereafter, the counts were taken at daily intervals until radioactivity had been absent over the thigh for one or more days. All counts were corrected for the room background and for the rate of disintegration of I^{131}.

In some cases 5 or 6 days after the first count when radioactivity over the thigh had disappeared 25 or 30 mg. thyrotropic hormone* (10 U.S.P. units) were given intramuscularly in a single dose on 1 or 2 successive days. Forty-eight hours later I^{131} was again administered intravenously and the uptake measured.

Types of Curves

Normal Uptake: Chart 1 shows the uptake curves of normal children who had received no thyroid therapy. The curves represent the counts over the neck minus the

* Gratitude is due the Armour Laboratories for a generous supply of lyophilized thyrotropin.

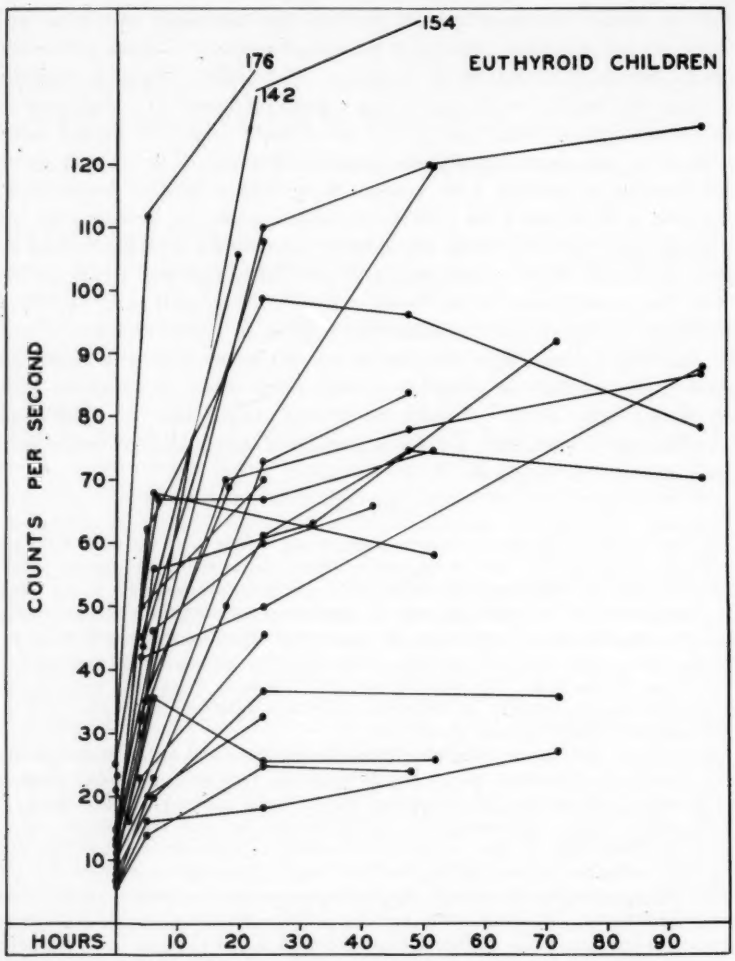

CHART 1. Measurements of radioactivity over neck after intravenous injection of tracer dose of I^{131} in euthyroid children.

counts over the thigh plotted against the time following the injection of I^{131}. Both counts were corrected for the rate of disintegration of I^{131}. The counts over the thigh, representing the I^{131} in the general circulation, generally fell progressively and disappeared after 24 to 48 hours. Over the neck the counts rose fairly rapidly during the first six hours and then more slowly, reaching a plateau of 30 to 150 counts per second at 24 to 48 hours. When corrections were made for disintegration the counts over the neck remained high for many days showing only a gradual decline. It is apparent that there was a considerable variation in the height of the plateau, representing the total accumulation of radioiodine. The curves are in essential agreement with findings of other workers.

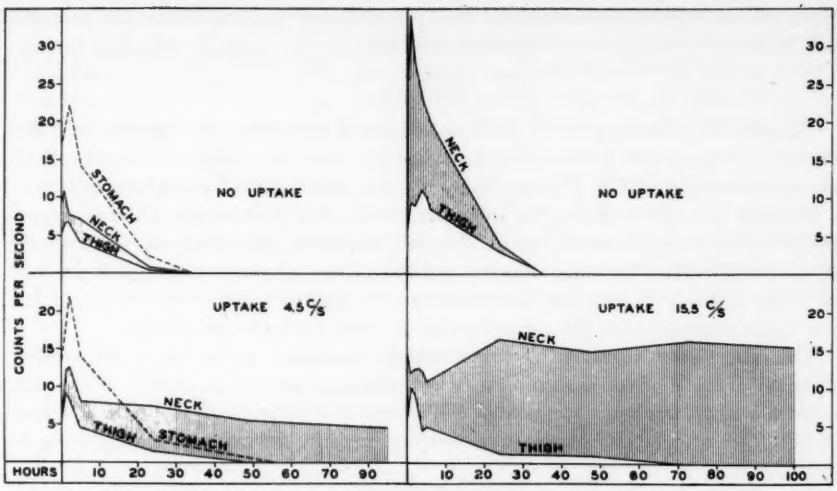

CHART 2. Measurements of radioactivity after intravenous injection of tracer dose of I^{131}. Upper curves showing disappearance of radioactivity over neck simultaneously with its disappearance elsewhere in body indicate absence of any thyroid tissue capable of trapping iodine. Lower curves showing persistence of radioactivity over neck long after it has disappeared elsewhere in body indicate presence of some thyroid tissue capable of taking up and retaining iodine.

No Uptake: In Chart 2 the upper two curves are the type which the authors believe indicate the absence of any significant uptake of radioiodine by the thyroid gland. Both the counts over the neck and those over the thigh (corrected for disintegration) were plotted against time. It is seen that the counts over the thigh began to fall promptly, due to disappearance of the iodine from the circulation. However, the counts over the neck rose during the first few hours and then fell, approaching those of the thigh and disappearing at about the same time in 24 to 48 hours. It is probable that the early elevation of the neck count is due to salivary excretion of I^{131} in the esophagus and the authors have been able to demonstrate a high degree of radioactivity in the saliva. The still higher count over the stomach is probably due to the presence of I^{131} in saliva and gastric juice.

Slight Uptake: In contrast, the lower curves of chart 2 show small counts over the neck persisting for many days after all radioactivity disappeared from the thigh and other parts of the body. It is believed that the persistence of such a count indicates the presence of a small amount of thyroid tissue capable of taking up iodine.

SELECTION OF CASES

Studies of I^{131} uptake have been made on 34 patients who had definite clinical and biochemical signs of hypothyroidism. Fourteen of these patients who had been treated previously with desiccated thyroid or were receiving it at the time of the study showed no uptake of I^{131}. Nine of the 14 were retested 48 hours after the injection of 30 mg. thyrotropic hormone and were again found to have no uptake. Since it was considered impossible to conclude whether some functioning thyroid tissue may have been present originally and undergone atrophy as a result of long continued treatment, these cases were excluded from the present study. Of the remaining 20 cases to be reported, 16 had

never received thyroid medication, but four patients (10, 11, 13 and 20) who were able to accumulate I^{131} in spite of treatment are included.

Results

"Congenital" Hypothyroidism: Table 1 lists 14 patients who had symptoms of hypothyroidism dating from birth or before the age of 12 months. Eight of these showed no measurable uptake of I^{131}, 4 (Cases 9, 10, 11, 12) showed small uptakes amounting to a retention over the neck of 3 to 16 counts/second, 2 (Cases 13 and 14) had normal uptakes of 90 and 95 counts/second. Two of the patients (Cases 10 and 13) showing uptakes had received thyroid previously and one (Case 11) was receiving it at the time of study. In the 8 cases (Cases 1, 2, 6, 9, 10, 11, 12, 14) in which the uptake of I^{131} was again measured after the administration of TSH, there was no increase.

The cases were reviewed to determine whether variations in the history and symptomatology of the disorder were correlated with differences of uptake of I^{131}. In the eight cases in which there was no uptake of I^{131} (Cases 1 to 8) marked symptoms of typical cretinism were apparently present from birth or the early months of life. In addition to

TABLE 1

Cases of Hypothyroidism Present at Birth or Beginning in Early Months of Life

Case	Onset of Symptoms	Age of Diagnosis	Condition when Studied			Thyroid Gland	Previous Thyroid Treatment	I^{131} Uptake counts/sec.§	
			Chron. Age	Bone Age	Chol. mg./100 cc.			Without TSH	After TSH
1*	Birth	2 mo.	2 mo.	<Birth	204	Not Palpable	None	0	0
2	"	3 mo.	3 mo.	<Birth	160	" "	"	0	0
3	"	4 mo.	4 mo.	<Birth	140	" "	"	0	
4	"	4 mo.	4 mo.	<Birth	216	" "	"	0	
5	"	8 mo.	8 mo.	<Birth	195	" "	"	0	
6	"	8 mo.	8 mo.	<Birth		" "	"	0	0
7*	"	24 mo.	24 mo.	<Birth	250	" "	"	0	
8	"	20 mo.	20 mo.	3 mo.	766	" "	"	0	
9	<1 yr.	21 mo.	21 mo.	4 mo.	474	" "	"	4	5.5
10*	<6 mo.	24 mo.	24 mo.	<3 mo.	448	" "	32 mg./day disc.† 2 mo. previously	16	8
11*	<1 yr.	21 mo.	8½ yr.	8½ yr.	240	" "	Receiving 96 mg./day	5.5	6.5
12*	3 mo.	4¾ yr.	4¾ yr.	9–12 mo.	344	" "	None	3	3.1
13*	Birth	11 mo.	3 yr.	9 mo.	420	Normal Size	32 mg./day disc.‡ 10 days previously	90	
14*	Birth	6¼ yr.	6¼ yr.	1¾ yr.	420	Enlarged	None	95	92

* Case histories appended.

† Patient had received 16 to 32 mg. desiccated thyroid daily during January at age of 21 mo.; study made in April.

‡ Received desiccated thyroid 32 mg. daily from 11 to 34th month; no treatment for 10 days prior to study.

§ "Counts/sec." indicates the count (corrected for disintegration) persisting over the neck after radioactivity had disappeared over the thigh.

coldness and circulatory mottling of the skin and constipation these patients at an early age had puffy myxedema of the face and large thickened tongues. In six cases the cretinoid appearance was so obvious that the diagnosis was made between the ages of 2 and 8 months. In the other 2 cases (Nos. 7 and 8) the clinical picture was also characteristic but the diagnosis was not made until the second year of life due to the fact that the infants were not taken to a physician.

In the four patients who showed a slight uptake of I^{131} (Cases 9, 10, 11, 12) the history indicates a somewhat slower, more insidious onset of symptoms, and three of the children did not present the grotesque, puffy appearance typical of cretins. Nevertheless, the fact that prior to treatment two of these patients had an osseous development of less than six months and that the other two showed typical epiphysial dysgenèsis in the head

TABLE 2

CASES OF ACQUIRED HYPOTHYROIDISM

Case	Onset of Symptoms (yr.)	Age of Diagnosis (yr.)	Condition when Studied			Thyroid Gland	Thyroid Treatment	I^{131} Uptake counts/sec.†	
			Chron. Age (yr.)	Bone Age (yr.)	Chol. mg./100 cc.			Without TSH	After TSH
15*	3–4	5¼	5¼	3	618	Not Palpable	None	0	80
16	3–4	8	8	4	560	" "	"	15.5	16.4
17	3–4	12¾	12¾	5½	406	" "	"	3.5	3.3
18*	5–6	11	11	6½	500	" "	"	4.0	5.4
19	10–12	15	15	12½	400	" "	"	3.7	2.4
20	1–4	12½	28	Adult		" "	Receiving 96 mg./day	18.5	19.5

* Case histories appended.

† "Counts/sec." indicates the count (corrected for disintegration) persisting over the neck after radioactivity had disappeared over the thigh.

of the femur and other early centers indicates that the thyroid deficiency had begun in the early months of life.[23]

Two patients (Cases 13 and 14) who had definite evidences of hypothyroidism dating from birth or shortly thereafter showed normal uptakes of I^{131}. In Patient 13 a thyroid gland of normal size and consistency was palpated. Patient 14 had a thyroid gland which was firm and enlarged to 1½ the normal size. The enlargement was not discovered until she was 6 years of age but may have been present from birth since it was visible only when she tilted back her head.

Acquired Hypothyroidism: Table 2 shows the findings in six patients who had the acquired type of hypothyroidism. Five of these patients had not been treated prior to the study, and one (No. 20) had received thyroid therapy for 14 years. The "time of onset" of the thyroid deficiency was based on the history and on the facts that growth and development had been entirely normal up until this time, that osseous development had advanced only very slightly beyond the time indicated, and that dysgenesis of the earlier epiphyseal centers was absent.

Five of the patients (Cases 16 to 20) showed a definite but small uptake of I^{131} ranging from 3.5 to 18.5 counts/second. The administration of TSH caused no increase

in the uptake when a second injection of I^{131} was given 48 hours later. The sixth patient (No. 15) showed no uptake of I^{131} when first studied, but 48 hours after the administration of 30 mg. TSH there was a normal rapid uptake of I^{131} causing a maximum count of 80/sec. This patient differed from the other ones in the fact that the thyroid deficiency was of shorter duration, probably about 1½ years in contrast to 4 to 8 years in the other cases.

Discussion

In this study the authors have assumed that after the administration of I^{131} the persistence of radioactivity over the neck for several days or longer after it can no longer be detected elsewhere in the body is evidence that some thyroid tissue is present. Although the amount of radioactivity retained is shown in the tables as "counts/second," the patients were classified merely as those having "no uptake," "small uptake" or "normal uptake," realizing that with this technic minor differences in the count may depend upon factors other than the amount of iodine-accumulating thyroid tissue present. In a patient who has previously been treated the absence of I^{131} uptake over the neck even after TSH does not prove that functioning thyroid is entirely lacking, since the uptake may be suppressed by the administration of thyroid or iodine, or the gland may have undergone atrophy as the result of long continued treatment. Since all patients having no uptake who had received thyroid or iodine were excluded, it is probable that the patients reported here as showing no retention of I^{131} were actually lacking in functioning thyroid tissue.

The 20 patients studied all showed marked hypothyroidism. In spite of the fact that no differences in the degree of deficiency could be detected by studies of the circulation, serum cholesterol or B.M.R., 9 patients showed no uptake of I^{131}, 9 had a small uptake and 2 a normal uptake. Unfortunately the authors were unable to make measurements of the protein-bound iodine of the serum or of the PBI^{131}.

The four patients believed to have the congenital form of the disorder who took up small amounts of I^{131} (Cases 9, 10, 11, 12) differed from those who showed no retention in that the clinical picture had developed more slowly and insidiously and that the typical myxedematous, cretinoid facies were absent. This suggests that the more typical cretins were born without any thyroid tissue while those with milder symptoms may have had small amounts with sufficient activity to delay the development of the clinical picture during the earliest months of life. The absence of increased uptake of I^{131} after the injection of thyrotropic hormone indicates that the thyroid tissue present was not capable of responding to stimulation.

The two patients who took up normal amounts of I^{131} are of special interest. The histories, the occurrence of epiphysial dysgenesis in the early centers and the marked immaturity of osseous development indicated that the thyroid deficiency had been present from birth or the earliest months of life. Patient 13 apparently had a thyroid gland of normal size and consistency while Patient 14 had a goiter of moderate size which may or may not have been present since birth. There was no indication of iodine deficiency in either case. Apparently the thyroid gland was unable either to convert inorganic iodine to thyroxine or to secrete the hormone if it were formed. Stanbury[13,14] studied three siblings and a child in another family with marked congenital hypothyroidism, who had developed large nodular goiters at the ages of 7 to 13 years. They lived on the Atlantic seaboard and received diets abundant in iodine. In each case large amounts of I^{131} were accumulated by the goiter. However, the oral administration of 1 or 2 gm. KSCN 4 to

27 hours after the I^{131} was given caused a sudden decrease in the radioactivity of the gland. He interpreted this as indicating that the inorganic iodine in the thyroid had not been bound into an organic compound and was released by the KSCN. In Patient 13 the effects of KSCN were not studied, but in Patient 14 the authors failed to demonstrate the rapid release of radioactivity from the gland described by Stanbury. This patient was given 0.5 gm. KSCN five hours after the administration of I^{131}. The count which was 94 per second showed no decrease and at the 18th hour the administration of 1.5 gm. again failed to cause a decrease. Seven days later the uptake of I^{131} was measured 48 hours after the administration of 30 mg. TSH. The uptake did not differ materially from the first study. On this occasion the oral administration of 1.5 gm. KSCN 3½ hours after I^{131} caused only a transient small decrease in the neck count. The authors have no explanation of these findings.

In five of the cases of acquired hypothyroidism (Cases 16 to 20) the uptake of I^{131} indicated that small amounts of thyroid tissue were present, in spite of the fact that the gland could not be palpated. However, the thyroid glands were apparently incapable of responding to stimulation with thyrotropic hormone in the doses given. Patient 15 had no uptake of I^{131} on the first test but after the administration of thyrotropic hormone showed a normal uptake and a clinical response consisting of increased pulse rate and general activity lasting for 4 or 5 days. This suggests that the hypothyroidism may have been due to deficiency of thyrotropic hormone rather than to a primary disorder of the thyroid gland. Werner[7] and other[21,22] believe that absence of response to thyrotropic hormone indicates a primary disturbance of the thyroid gland while a positive response is evidence that hypothyroidism is secondary to pituitary dysfunction. Certainly if there were a pituitary disturbance in this patient, it must have been limited to a specific deficiency of thyrotropin since she showed no other signs of hypopituitarism and during the past four years thyroid therapy has brought about entirely normal growth and development, a result which does not occur in the usual cases of generalized hypopituitarism. The hypothyroidism was of much shorter duration in this patient than in any of the other cases of acquired type studied. It is possible that in some of the other cases of longer duration the initial failure may have been due to deficiency of thyrotropic hormone and subsequently the gland may have atrophied to a degree when it was no longer capable of responding to stimulation.

The studies reported suggest that in congenital hypothyroidism due to defective development of the gland there are differences in the degree of the defect. In patients in whom no thyroid tissue can be demonstrated clinical symptoms appear earlier and are more striking than in patients in whom a small amount of tissue capable of accumulating iodine can be found. In addition some patients who have unquestionable signs of hypothyroidism and live in regions where iodine is abundant can be shown to have thyroid glands which are either of normal size or enlarged and which are capable of taking up iodine normally but are unable to secrete adequate amounts of hormone. Additional studies of the dysfunction are being made.

Abstracts of Illustrative Histories

Patients with Marked Symptoms of Cretinism From Birth and No Uptake of I^{131}

Case 1. It was noted at birth that the infant had a peculiar bloated appearance with puffy features, short fat neck and depressed nasal bridge. The tongue was thick and protruded so that he had difficulty breathing and feeding. His hands and feet were always cold and the skin was dry, dusky and

mottled. The bowels were always constipated. When examined at 2 mo., he presented a typical cretinoid appearance. The epiphysial development was less than normal for a newborn infant and there was characteristic dysgenesis of the cuboid of the foot.

Case 7. From the time of birth, the child was inactive, and his skin was dusky, mottled and cold. He was chronically constipated. An umbilical hernia was present. He took his feedings poorly and grew and gained very little. He took little interest in his environment. The first tooth erupted at 21 mo., and he was unable to sit alone at 2 yr. When first examined at 2 yr., he presented a characteristic cretinoid appearance. The height age was 5 mo. His osseous development had not progressed beyond the birth level and there was dysgenesis of the epiphyses at the knee.

Patients with Insidious Onset of Symptoms of Hypothyroidism During Early Months and Slight Uptake of I^{131}

Case 10. This boy was slow in his growth and development. He sat alone at 14 mo., cut his first first tooth at 17 mo. and began to walk at 23 mo. At 20 mo., his osseous development was that of a newborn infant. However, he had always been fairly alert and active, and numerous photographs showed that he did not have a cretinoid facies and was not puffy or myxedematous. Thyroid treatment with doses of ¼ to ½ gr. daily was given at 21 mo. for a few weeks, but it was discontinued 2 mo. prior to the I^{131} study. The serum cholesterol was 448 mg./100 cc.

Case 11. This child was considered normal and showed nothing unusual in the character of her features, skin or color until she was about 1 yr. of age. However, no teeth erupted until she was 13 mo. After she was 1 yr. of age, she became progressively more apathetic and ceased to grow or develop. A second tooth erupted at 15 mo. but no more appeared until the 21st mo. At the age of 21 mo. her height age was 10 mo., bone age 6 mo. Her features were not coarse or cretinoid. Thyroid therapy was begun at this time and caused marked clinical response with accelerated growth and development. The I^{131} study made when she was 8¼ yr. old showed a moderate uptake in spite of the fact that she had been receiving thyroid 1½ gr. daily for the past 6½ yr.

Case 12. The patient seemed normal at birth. At 3 mo. it was noted that the skin had a yellowish tinge. She sat alone at 7 mo. and walked at 18 mo., but she was relatively inactive and tired easily. The first teeth erupted at 14 mo. At 2 yr. she became chronically constipated. After 3 yr. the mother noticed that she was growing very little. When examined at 4 yr., 10 mo., she did not have characteristic cretinoid features but had an infantile type of naso-orbital development. Her height age was 3 yr. The osseous development showed scattering between the levels of 9 mo. and 3 yr. with an average development of 9 to 12 mo. All the postnatal centers including the head of the humerus (3 mo.) and the head of the femur (9 mo.) showed dysgenesis.

Patients with Onset of Hypothyroidism in Early Months Who Had Normal or Enlarged Thyroid Glands and Showed Normal Uptake of I^{131}

Case 13. This boy had been slow in his growth and development. The first tooth had erupted at 13 mo.; he sat alone at 13 mo. and walked at 18 mo. He had had a poor appetite but was not constipated. His features had never become puffy or cretinoid. When he was examined elsewhere at 11 mo. his height age was 5 mo. and no postnatal centers had ossified. From 11 to 34 mo. he was treated daily with ½ gr. of desiccated thyroid or less. When he was studied at 2 yr., 11 mo., his height age was 2 yr. and his bone age was 9 mo. At that time thyroid had been omitted for 10 days, and there were circulatory changes and coolness of the skin suggestive of hypothyroidism but there was no myxedema. The serum cholesterol was 420%. A number of examiners thought that his thyroid gland was of normal size and consistency. Certainly no goiter was visible or demonstrable on roentgenographic examination of the mediastinum. Following the demonstration of a normal uptake of I^{131} he was allowed to continue without thyroid therapy for another 7 wk. in order to establish the diagnosis more conclusively, at the end of which the cholesterol had risen to 460 mg./100 cc.

Case 14. There was no history of any thyroid disturbance in the family and the patient had 2 normal siblings. She had always lived in Baltimore and had taken a normal diet. She seemed normal at birth but during the 1st 2 wk. of life had a severe attack of epidemic diarrhea of the newborn infant with jaundice. The first teeth did not erupt until she was 15 mo. old, and she did not walk until the age of 2 yr. She grew slowly. She was relatively inactive and phlegmatic and was

constipated. Her color was always pale and slightly yellowish. When she was 6 yr. old an enlargement of the thyroid was noticed for the first time. When she was examined at the age of 6¼ yr., her height age was 3 yr. and her bone age 1¾ yr. There was dysgenesis of the heads of the femora and humeri. Her skin was pale and cool and the musculature flabby. There were no signs of myxedema. The serum cholesterol was 420 mg./100 cc. The thyroid gland was diffusely enlarged and firm, about 1½ times the normal size, but it was apparent only when she tilted back her head. After diagnostic studies were completed an excellent therapeutic response to desiccated thyroid confirmed the original impression of hypothyroidism.

Patient with Acquired Hypothyroidism of 1½ Years' Duration Who Showed No Uptake of I^{131} Before TSH and Normal Uptake After Its Administration

Case 15. The child had grown and developed normally and had been active, energetic and alert with regular bowels and good color up until the age of 4 yr. At that time her appetite became poor and she stopped gaining. She became sluggish and apathetic. Her color became pasty; the skin cold and dry; the bowels constipated. When she was examined at the age of 5½ yr., her height age was 4 yr., bone age 3½ yr., mental age 5 10/12 yr. She was placid and inactive. The skin was cool and pale with circulatory mottling. She was slender and showed no puffiness or myxedema. The serum cholesterol ranged between 618 and 467 mg./100 cc.; the B.M.R. was −28%. I^{131} studies were made before starting treatment. Subsequently thyroid therapy has resulted in entirely normal growth and development.

Patient with Acquired Hypothyroidism of 4 to 5 Years' Duration Who Had No Uptake of I^{131} Before or After TSH

Case 18. This boy had been entirely normal and was lively and energetic until he was 5 yr. of age. The first dentition, walking and talking had occurred at the average time. He had had good color and regular bowels. Linear growth had been normal until 5 yr. after which it gradually slowed, although his short height did not attract attention until he was 9 yr. After 5 yr. he gradually became less energetic and was constipated. His color became pale and his skin dry and cool. None of the deciduous teeth were lost until he was 10 yr. old. Because of his pallor he was treated for anemia between the ages of 9 and 11 yr. When he was examined at 11¼ yr. he was slow and apathetic. His skin was cold, pale, slightly yellowish. The tissues were loose and flabby although there was no obvious myxedema. The height age was 6¾ yr., the bone age 6½ yr. with suggestions of epiphysial dysgenesis in some of the 4 yr. centers, but not in the earlier ones.

Summary

A method for demonstrating small uptakes of radioiodine by the thyroid gland has been described. The study suggests that in some cases of cretinism iodine-accumulating thyroid tissue may be completely absent while in others a small amount may be present. In cretins in whom a small amount of thyroid tissue can be demonstrated, the symptoms, even though appearing during the first year of life develop more insidiously. In cases of hypothyroidism developing later in childhood, small amounts of thyroid tissue capable of taking up iodine usually can be demonstrated.

In addition to the cases of hypothyroidism in which there is absence of the gland or marked diminution in the amount of thyroid tissue, two patients (Nos. 13 and 14) with definite hypothyroidism showed a normal uptake of I^{131}. One of those patients had a thyroid gland of normal size, the other a moderately enlarged gland. They lived in regions in which there was no likelihood of deficient iodine intake (see Addendum).

One patient (No. 15) with acquired hypothyroidism took up no iodine when first studied but after injection of thyrotropic hormone showed a normal uptake. The problem of whether acquired hypothyroidism may be due to deficiency of thyrotropic hormone is discussed.

Addendum

Since the completion of this paper a number of other patients with congenital hypothyroidism whose thyroid glands were capable of accumulating iodine normally have been discovered. The cause of this type of hypothyroidism and the subsequent development of goiter and neoplasm when treatment is inadequate will be the subject of a subsequent report.

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SPANISH ABSTRACT

Fijación de Yodo Radioactivo en el Estudio de Diferentes Tipos de Hipotiroidismo en la Infancia

Este trabajo se realizó buscando una explicación a las desviaciones tan marcadas de la sintomatología de niños hipotiroideos así como para tratar de aclarar las diferencias etiológicas. Las divergencias clínicas entre cretinos congénitos y niños con hipotiroidismo adquirido, dependen en gran parte del grado de desarrollo del paciente antes de iniciarse el trastorno glandular; sin embargo, a menudo se observan diferencias notables en el cuadro clínico de hipotiroideos no tratados, de dos a tres años de edad, con desarrollo óseo apenas sobrepasando al del nacimiento, lo que indica que la deficiencia existe desde el nacimiento; en estos casos es imposible a menudo demostrar las deficiencias tiroideas por los métodos comunes de estudio de cambios circulatorios, colesterol sanguíneo, metabolismo basal y del yodo proteíco. Se acepta que la investigación de la fijación del yodo radioactivo no demuestra la capacidad funcional de la tiroides para secretar hormona, pero sí podría demostrar la presencia o ausencia de tejido tiroideo; y la existencia de tal tejido, determinar las manifestaciones de los cuadros clínicos discretos; asímismo podrían hallarse casos con deficiencia tiroidea debida más a la incapacidad de la glándula para sintetizar la hormona que a la ausencia misma de esta glándula.

El estudio de la fijación del yodo radioactivo se hizo en 34 pacientes con signos clínicos y bioquímicos definidos de hipotiroidismo; los autores asumieron que después de la administración de yodo radioactivo (I^{131}), la persistencia de radioactividad en la región tiroidea tras de varios días de no encontrársele en otro sitio del organismo, demostraría la presencia de alguna porción de tejido tiroideo.

Los autores describen el método para investigar la fijación del yodo por la glándula tiroides.

El estudio sugiere que en algunos casos de cretinismo se puede encontrar pequeña cantidad del tejido tiroideo y que en otros puede no hallarse en lo absoluto; en los primeros aparecen los síntomas insidiosamente aún dentro del primer año de vida; en casos de hipotiroidismo de aparición durante la infancia, generalmente se encuentra tejido tiroideo capaz de fijar el yodo.

Dos casos de hipotiroidismo definido mostraron una fijación normal de yodo radioactivo; uno de ellos mostró una tiroides de tamaño normal y el otro moderadamente crecida; ambos vivían en regiones sin posibilidades de fijación deficiente de yodo (casos números 13 y 14).

Otro caso con hipotiroidismo adquirido no absorbió yodo durante el primer estudio pero tras de una inyección de hormona tirotrópica tuvo una respuesta normal.

Se discute el problema de si el hipotiroidismo adquirido se debe a la deficiencia de la hormona tirotrópica.

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VESTIBULAR RESPONSES TO ROTATION IN THE NEWBORN INFANT

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THE need for exact knowledge of the normal vestibular response of young subjects to artificial stimulation became apparent to one of the authors while testing a group of patients with H. influenzae meningitis who had been treated with streptomycin. In addition to its importance in detecting vestibular damage caused by streptomycin, such information is of value in examining the cranial nerves of the newborn infant to identify congenital defects and birth injuries, and at later ages to confirm the presence of postnatal injuries and diseases.

To date, evaluation of the normal vestibular function in the newborn and young infant has been inadequate. This study is an attempt to perfect a technic or appraise the results of a simple vestibular test in infants and children.

This report concerns the vestibular response of 64 newborn infants to various stimuli. These infants were all healthy and were considered normal. Their ages varied from 3 hours to 10 days, and their weights between 2.2 to 4.0 kg. Sex and cultural background were disregarded. Caloric tests proved unsatisfactory at this age, because of smallness of the external canal and apparent discomfort to the infants manifested by their crying and tight closing of eyes, which made observation of nystagmus impossible. The following gives methods and results of rotation testing.

METHOD

The rotation apparatus used consisted of an electrically driven turntable actuated by a D C ¼ H. P. motor, capable of turning in either direction and with a rheostat speed control. With its full load it was routinely accelerated to 30 rpm in 180° and braked to a stop in 45°. This table had been used in a previous streptomycin toxicity study[1] and was modified to accommodate a well padded baby holder. The infant was placed supine on the platform (Fig. 1), with the head over the center of rotation. The head was extended 60° from the frontal plane of his body, so as to place the lateral semicircular canals in the plane of rotation, and was held between 2 loose padded muffs which allowed about 45° of rotation. The babies were rotated 10 times in 20 sec. Following a rest period of 3 to 5 min., rotation was repeated in the opposite direction.

The eyes were inspected before, during and after rotation. Eye deviation, nystagmus, head, neck and general body responses were noted.

RESULTS

The usual movements of the eyes before the beginning of rotation were slow and roving. Immediately after the onset of rotation the head turned in the opposite direction of rotation in all but 6 of the 64 cases. These 6 showed no movement. After a few turns

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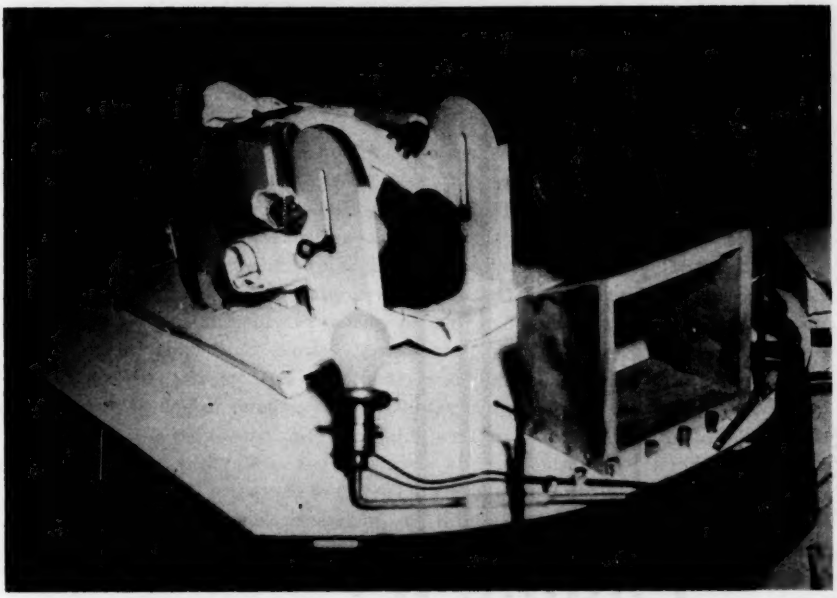
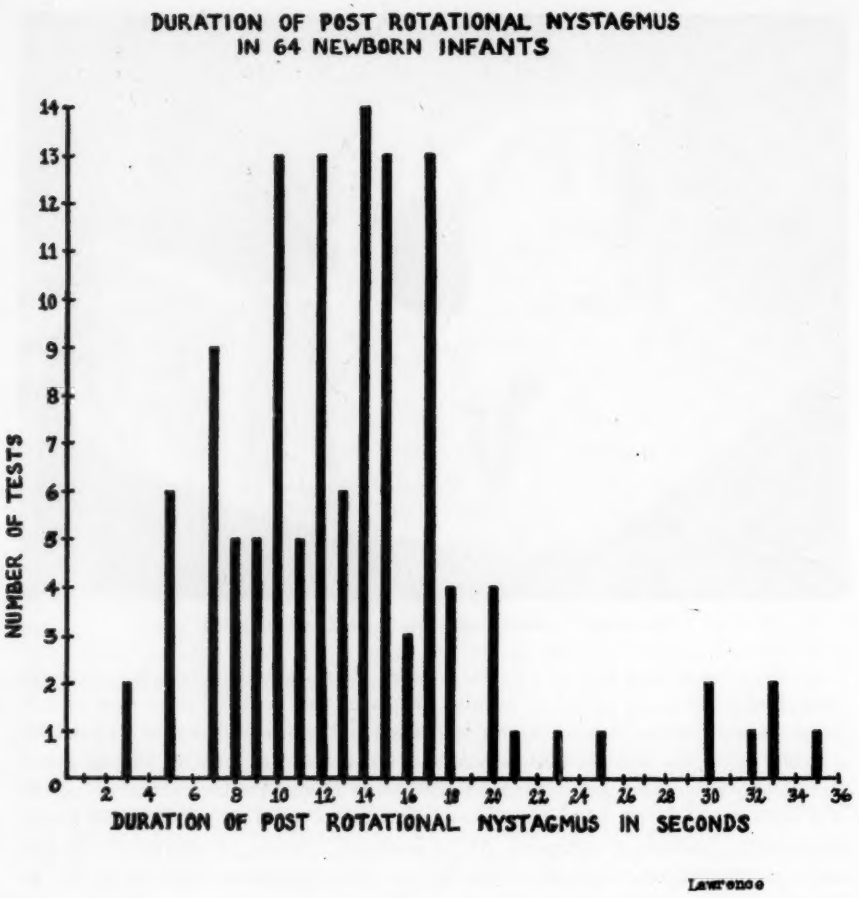


FIG. 1. Male infant on turntable in position for rotation.

many of the heads came back to a central position. Fifty-two of the infants kept their eyes open during the entire period of rotation. The eyes and heads of these were seen to deviate in the opposite direction to that of rotation and in this quadrant the eye exhibited a regular nystagmus with the fast component in the direction of rotation. This nystagmus started with acceleration and continued several turns. During the later period of rotating at a constant speed, the eyes in most cases returned to center or assumed their pretest roving with cessation of nystagmus. At the instant of braking (deceleration) the head and eyes rotated to the direction of turning and again nystagmus started, with the fast component now opposite to the direction of turning. Nystagmus, to acceleration and deceleration, was observed in 100% of the 64 cases. It was variable in rate and intensity but its direction was always parallel to the plane of rotation. Graph 1 contains a plot of the duration of postrotational nystagmus versus number of tests in 64 infants who were awake during the test. The duration of postrotational nystagmus varied from 3 to 35 seconds, and in any individual infant, was equal or within a few seconds in either direction except in three cases which were not further followed. It is probable that the reading of three seconds is inaccurate because the infant in whom it was observed had a 20 second response in rotation in the other direction, a value which according to the authors' findings is normal. The average postrotational nystagmoid response to 10 turns in 20 seconds was 13.1 seconds. Skin flushing, eructation and voiding were frequent during rotation. The above observations were checked by taking 16 mm. movies of a sizeable cross-section of the babies before, during, and after rotation. The movie camera and lights were rotated with the baby and included a picture of his face. (See Fig. 1.)

Eight infants were rotated both asleep and awake. The method used to observe the



GRAPH 1

eyes of all sleeping infants was as follows: An observer stood at the exact spot where the machine was stopped. The observer then separated the infant's eyelids and watched the eyes for a full minute. None of the babies who were asleep during the test had any post-rotational nystagmus, nor did five others not included in the series of 64, who were rotated asleep only. The eight infants were also described in the preceding awake group.

Failure to respond to vestibular stimulation during sleep was previously observed by one of the authors in a 4½ month old infant who did not respond to 30° or 44°C. water (Hallpike Fitzgerald test), to rotation at 60 rpm, nor to 100 cc. of ice water in one ear. The child remained sound asleep during all of the above procedures, but during irrigation of the second ear with ice water the child stirred and awakened. At this time, the eye under observation, which had been rolled up, came down and immediately went into regular rapid medium nystagmus. The other tests repeated while awake were all within normal limits. In the series of 64, there was no difference in response in relation to age or weight.

The authors have found this method of rotation a useful one for the study of vestibular function in the newborn infant. The apparatus used is simple to construct, convenient to manage, and gives consistent results, in contrast to hand rotation using the Bárány chair.

Comment

Few references to vestibular responses in the newborn infant can be found in the literature and the reports are conflicting as to the presence of nystagmus. Ford[2] states that reactions to rotation or rotary acceleration are present at birth. However, he does not describe these responses. Magnus,[3] in his description of responses to rotation in newborn animals, found that nystagmus could be observed at 18 days in the rabbit, at 4 or 5 weeks in the dog and at 6 and 7 days in the cat. Bartel[4] described eye deviation but no fast component of nystagmus in newly born premature human infants; full term newborn infants, on the other hand, showed normal nystagmus in response to rotation. DeKleyn and Schenk[5] in 1931 reported their findings on rotating a one week old anencephalic child. Their method of rotation was to hold the infant by the trunk with his head in the upright position; the observer and the child then turned about a vertical axis. Turning to the right caused a postrotation fast component of nystagmus to the left; likewise rotating to the left resulted in nystagmus to the right. This infant, as shall be commented on later, lacked cerebral hemispheres, cerebellum, and third and fourth nerve nuclei.

McGraw,[6] as a part of a more comprehensive study, observed the postural and ocular responses of the infant to bodily rotation. This study included 67 infants from birth to 2 years. The child was held in an upright position facing the experimenter, and both turned together, the experimenter pirouetting. No attempt was made to stimulate "particular vestibular canals." The speed of turning was calculated to be 0.778 rotations per second; body and ocular deviation were recorded by direct observation. Three types of response were described: A phase during which the eyes deviated laterally in the direction of rotation during the movement and in the opposite direction after rotation had ceased; this "phase" occurred in 100% of the infants under about one month of age. A gross oscillatory phase (Phase B) at about the fourth month in which the eyes showed coarse slow horizontal excursion during rotation, continuing for a few seconds after rotation was stopped. A fine oscillatory phase (Phase C) during rotation, occurring around the seventh month. No mention was made of how optokinetic nystagmus was eliminated during rotation in the older age group. Also there was no control of acceleration, speed or deceleration with this method.

McGraw[7] posits that the "changing adjustments of the infant to rotation indicate reorganization of the neural system involved," and states that there is considerable doubt that the cerebral cortex exercises much influence upon these labyrinthine reflexes. Ford,[2] on the basis of the work of Langworthy,[8] states that "with some exceptions the anatomical development of the segmental apparatus is complete at birth" and that "the chief supra-segmental structures and their projection paths are still immature." We should expect, then, that vestibular responses in the newborn infant would be purely a response of the archaic motor system, a name used by Gesell[9] for the early response systems, and that this archaic motor system would be free of cerebral inhibition. Again interpreting Langworthy's work, Ford states that the lack of cerebral function in the newborn infant is expressed in two ways: absence of true volitional activity and lack of inhibition of the segmental apparatus.

We should expect, too, that the vestibular system would be entirely capable of func-

tioning on its own since the neurons involved are among the earliest to become myelinated, beginning as early as a fetal age of 20 to 24 weeks (Langworthy). The neurons involved in nystagmus produced by stimulation of semicircular canals are the third, fourth, sixth, and the vestibular part of the eighth cranial nerves and the median longitudinal fasciculus. Furthermore, according to Langworthy, the sequence in which tracts become myelinated is correlated with the sequence in which the function of structure develops. The anencephalic child described by deKleyn and Schenk,[5] who at one week of age exhibited both components of nystagmus, proves the ability of this archiac vestibular apparatus to function independently of cerebral influence. Only the reflex connections, labyrinths, vestibular and abducens nuclei were present; the cerebral hemispheres, cerebellum, and third and fourth nerves were absent.

The group of 64 newborn infants described in this report can be compared to McGraw's newborn group. As has been noted, McGraw's newborn infants were said to show "Phase A" postrotation response consisting of head and eye rotation toward the direction opposite to that of rotation. The post-rotation findings of the present investigators were eye deviation to the direction of turning and a fast component (nystagmus) opposite to the direction of turning. The rotation apparatus used made it possible to observe the eye responses of infants with comparative ease and to obtain consistent results in this study. Other observers have reported eye movements in the newborn infant, in response to rotation, but they have not reported in detail concerning the presence of the fast component (nystagmus), its duration, direction and associated movements.

A careful review of the available reports on vestibular responses to rotation in adults reveals no work on an adult group comparable to that done by the present authors with newborn infants. Speed of rotation, rate of acceleration and rate of deceleration were all kept constant in the present study. None of the methods described in the rotation of adults has kept these factors constant. Because these important factors are variable, it is difficult to compare the results of these tests on adults with each other or with those done on this newborn group. Northington[10] describes a rotation test for adults in which the same semicircular canals are stimulated as in this study. In the adult test the individual is in a face-front seated position with the head flexed 30°. In both instances the horizontal semicircular canal is in the same plane as the plane of rotation. The Bárány chair used for testing adults is rotated by hand 10 times in 20 seconds. Northington[11] found that the duration of the postrotatory nystagmus varied from 15 to 31 seconds and in the majority from 15 to 20 seconds. The average postrotational nystagmus is 18 seconds in duration. In adults amplitude is usually rated as fine, medium or coarse, and the frequency as fast, medium or slow. These observations are rather inaccurate and vary with the observer. It is, however, the impression of one of the authors that the response in the newborn infant is of greater amplitude, slower frequency, and shorter in duration than in adults. The need for standardized and controlled rotation tests, and permanent recordings of eye movements is great. When these improvements are worked out and normal responses are tabulated for large groups, then vestibular tests will become more meaningful as a diagnostic aid. A permanent recording of eye movements other than motion pictures, but more like an EEG or ECG will eliminate the inaccuracies of observers and give exact measurements of duration, frequency and amplitude. At this writing several approaches to the problem are being investigated by Dr. Edmund P. Fowler, Jr.

Summary

Using a newly designed rotating apparatus with control of acceleration, deceleration and speed, the response of 64 full term newborn infants to rotation was studied.

While awake, all infants showed head and eye deviation opposite to the direction of rotation during acceleration and in the same direction during deceleration; all infants had a normal nystagmus during acceleration and for several turns of constant speed. Then followed a reversal of the nystagmus as soon as deceleration took place. The duration of postrotational nystagmus following 10 turns in 20 seconds varied from 3 to 35 seconds with an average of 13.1 seconds. There is no comparable adult group reported as the stimulus is not constant or controlled.

Sleeping infants had no response to rotation even though they gave normal responses while awake.

Associated postrotation reactions were: flushing, eructation and voiding.

The literature on vestibular responses to rotation in the newborn infant has been reviewed.

Acknowledgment

The authors wish to thank Dr. Edmund P. Fowler, Jr., for his guidance and sponsorship of this project.

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Spanish Abstract

Respuestas Vestibulares a la Rotación en Niños Recién Nacidos

Al examinar un grupo de pacientes con meningitis a hemofilus influenzae tratados con estreptomicina se vió la necesidad de conocer mejor la respuesta vestibular normal de los lactantes a la excitación artificial; al mismo tiempo que se analiza el daño causado por la estreptomicina se pueden estudiar los nervios craneales para identificar defectos congénitos, lesiones de nacimiento en el recién nacido, o bien confirmar la presencia de lesiones y enfermedades post natales en edades mayores. Los autores presentan este estudio como un esfuerzo para perfeccionar una técnica que valore los resultados de una sencilla prueba vestibular en lactantes y niños.

Se estudiaron 64 niños recién nacidos sanos y normales, con edades variables de tres horas a diez días y pesos de 2.2 a 4 kilogramos, sin considerar el sexo ni el grado cultural familiar.

Se empleó un aparato de rotación con control de la velocidad, tanto para aumentarla como

disminuírla o sostenerla; se rotó a los niños 10 veces en 20 segundos y después de un descanso de 3 a 5 minutos, la rotación se repitió en dirección opuesta. Se observaron los ojos, antes, durante y después de la rotación, anotándose desviaciones oculares, nistagmus, repuesta de la cabeza, del cuello y del cuerpo.

La literatura no presenta más que pocas observaciones de las resquestas vestibulares en el recién nacido y los informes son contradictorios en cuanto a la presencia del nistagmus.

Todos los niños examinados por estos autores mostraron durante la vigilia desviación de la cabeza y de los ojos en sentido opuesto a la dirección de la rotación durante la aceleración, y en la misma dirección durante la disminución de la velocidad; todos presentaron un nistagmus normal durante la aceleración y durante varias rotaciones a una velocidad sostenida, pero el nistagmus se invirtió al disminuír la velocidad. La duración del nistagmus después de 10 vueltas en 20 segundos varió de 3 a 35 segundos, obteniéndose un promedio de 13.1 segundos. No se tiene conocimiento de un estudio comparable en un grupo de adultos.

No se observaron respuestas a la rotación cuando los niños dormían a pesar de que su respuesta fué normal en la vigilia. Las reacciones observadas después de la prueba fueron: enrojecimiento, eructación y micción urinaria.

19 Hamilton Terrace

THE ROLE OF THE PULMONARY VASCULAR BED IN CONGENITAL HEART DISEASE

By J. FRANCIS DAMMANN, JR., M.D., AND WILLIAM H. MULLER, JR., M.D.
Los Angeles

LIFE expectancy and the degree of invalidism have been considered a function of the type of cardiac malformation in patients with congenital heart disease. When the abnormality involves a large communication between the ventricles or great vessels, however, the pulmonary vascular bed plays an important role in governing prognosis. The following group of congenital malformations are involved in this category: 1. single ventricle without pulmonary stenosis, 2. large ventricular septal defect, 3. Eisenmenger complex, 4. atrio-ventricularis communis, 5. true truncus arteriosus, 6. aortic septal defect, 7. large patent ductus arteriosus and 8. patent ductus arteriosus associated with coarctation of the aorta.

THEORETIC CONSIDERATIONS

Peripheral resistance in the systemic circulation is maintained chiefly by the arterioles. The caliber of these small muscular vessels is controlled by the autonomic nervous system. Changes in the caliber of the arterioles alter peripheral resistance and, hence, blood pressure. Normal systemic peripheral resistance is maintained at a high level, thus maintaining a relatively high systemic blood pressure. White[1] has stated that the range of normal adult systemic blood pressure is 145/95 to 90/60 mm.Hg. By using the simplified formula set forth by Friedlich,[2] (Resistance (mm.Hg/l./min./M^2 = $\frac{\text{Mean pressure (mm.Hg)}}{\text{Blood flow (l./min./}M^2\text{)}}$), the range of systemic resistance is found to be 37 to 23 mm.Hg/l./min./M^2.

In contrast to the systemic circulation, the normal pulmonary vascular bed is characterized by great distensibility of the arterial walls and a large capacity of the arterial and capillary beds. A low peripheral resistance and consequent low pulmonary blood pressure is the essential attribute of the pulmonary circulation. The great distensibility of the pulmonary vascular bed in the normal human is illustrated by the effect of increased pulmonary blood flow on pulmonary pressure. Cournand[3] showed that the pulmonary artery pressure does not rise above normal levels until the pulmonary blood flow exceeds three times the basal level. Normal values for pulmonary blood pressure are 19/6 mm.Hg to 26/12 mm.Hg; pulmonary resistance is 2 to 5 mm.Hg/l./min./M^2.[2] Definite proof of a vasomotor control of the small pulmonary arteries and arterioles is lacking. However, Zimmerman and his co-workers[4] demonstrated the vasoconstrictive action of adrenalin and the vasodilatation effect of aminophyllin on the pulmonary vascular bed. Whether this effect is humeral or nervous could not be stated. Hickam[5]

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demonstrated constriction of the pulmonary arteries during excitement and emotion. Motley and his associates[6] demonstrated a distinct rise in pulmonary artery pressure following short periods of induced acute anoxia. Normally, however, changes in pulmonary artery pressure are small as compared to changes in systemic pressure.

In the normal individual, then, the vascular bed offers a considerable resistance to blood flow in the systemic circulation and very little resistance to blood flow in the pulmonary circulation. If this difference were present when the two circulations were joined, as in the case of a single ventricle, it is readily apparent that the major portion of the cardiac output would be directed to the lungs and little to the body. Such a course would hardly be compatible with life.

Civin and Edwards[7] traced the development of the pulmonary vascular bed from a fetal to an adult state. They demonstrated progressive changes in the elastic arteries, the muscular arteries and the pulmonary arterioles. At birth elastic arteries are open but the walls are relatively thick as compared to the size of the lumen. With growth the wall becomes relatively and absolutely thinner and the lumen relatively and absolutely larger. At birth the lumens of the muscular arteries and arterioles are small and their walls are thick. With growth the media thins out and the lumen widens. These changes take place during the first few months of life and are completed for the most part by the age of 6 months.

It seems reasonable to relate these morphologic changes to changes in pulmonary physiology and to suggest that pulmonary vascular resistance falls as the pulmonary vessels thin out and widen. Although pulmonary arterial resistance and blood pressure have not been measured in normal humans at birth, there is evidence to suggest that they are high. Hamilton and his co-workers[8] found that the pressure within the right and left ventricles of the newborn rabbit and dog were essentially similar prior to and immediately after the first few breaths had expanded the lung. Barclay[9] demonstrated by means of angiocardiograms that the right ventricle supplied blood to the descending aorta through the ductus in the living sheep fetus. It is probable that the high pulmonary pressure immediately following birth is responsible for the absence of a murmur in infants with patent ductus arteriosus.

Edwards[10, 11] and Civin and Edwards[12] suggested that the pulmonary muscular arteries retain their fetal characteristics and high resistance in patients with certain types of congenital malformations of the heart. Furthermore, they have argued that, as a result of the high pulmonary resistance and consequent high pulmonary arterial pressure, secondary changes take place within the muscular pulmonary arteries causing a further reduction in lumen size and a further increase in resistance. These changes consist of the deposition of hyaline material in the intima and the fragmentation and necrosis of the elastic tissue and smooth muscle tissue within the media. They suggest that the maintenance of the fetal state is compensatory but that the secondary changes that occur in the intima and media, causing further increases in pulmonary resistance, act to the detriment of the patient. In a series of articles, Edwards and his co-workers have cited numerous examples including coarctation of the aorta proximal to the patent ductus,[11] the Eisenmenger complex[13] and single ventricle without pulmonary stenosis[14]; Adams[15] suggested that examples of simple septal defects be included as well. Goldberg and his associates[14] gave additional weight to the argument by presenting catheterization data on a case of Eisenmenger complex with an anomalous pulmonary vein entering the right auricle. The pulmonary venous pressure was found to be normal but the pulmonary arterial pressure

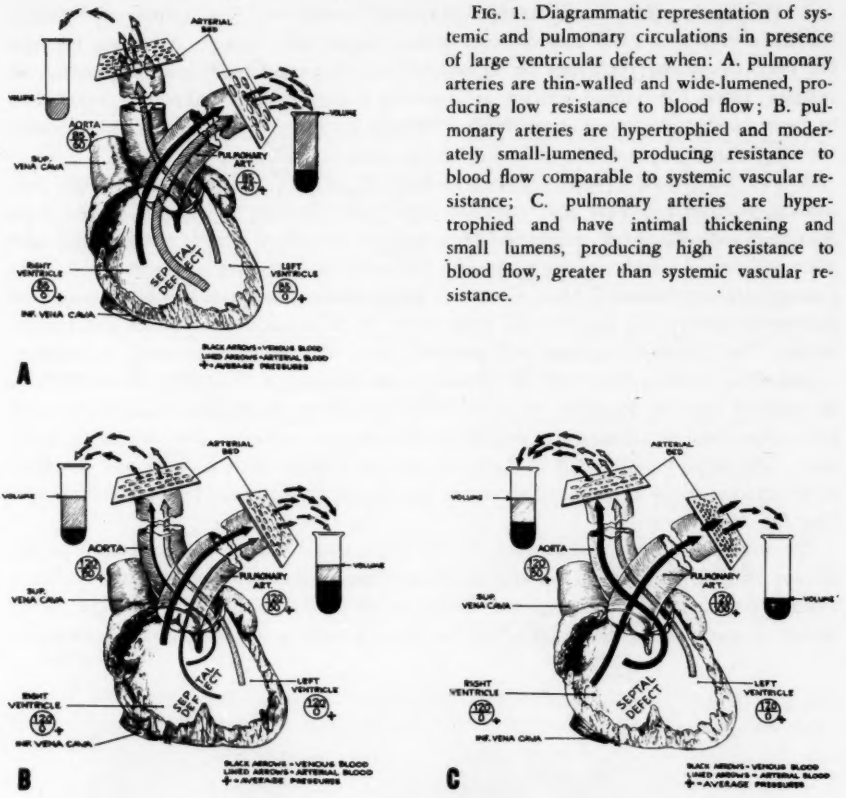

FIG. 1. Diagrammatic representation of systemic and pulmonary circulations in presence of large ventricular defect when: A. pulmonary arteries are thin-walled and wide-lumened, producing low resistance to blood flow; B. pulmonary arteries are hypertrophied and moderately small-lumened, producing resistance to blood flow comparable to systemic vascular resistance; C. pulmonary arteries are hypertrophied and have intimal thickening and small lumens, producing high resistance to blood flow, greater than systemic vascular resistance.

high and the pulmonary venous oxygen saturation was normal although saturation within the aorta was low. The present investigators have recently produced luminal narrowing, medial hypertrophy and intimal thickening in the small pulmonary arteries of dogs subjected to a large pulmonary blood flow and high pulmonary artery pressure. This will be reported in detail in a separate communication.

Theoretically, in patients with the type of congenital heart disease under discussion, there are three possible courses that the pulmonary vascular bed may follow after birth. 1. The thick-walled, small-lumened pulmonary vessels may retain their fetal characteristics for a period of months and then may gradually thin out and approach the adult type of pulmonary vessel. As the walls thin out and the lumens widen, pulmonary resistance falls. More blood will be directed out the pulmonary artery and relatively less blood to the aorta. To maintain systemic blood flow at a level compatible with life, either systemic resistance must fall or cardiac output must rise. Evidence obtained by catheterization indicates that cardiac output is high and systemic resistance is unchanged. If this sequence of events continues, high output cardiac failure ensues. The signs and symptoms in this group of patients are those due to pulmonary congestion and cardiac decompensation. Because of the high volume of pulmonary blood flow, cyanosis will be absent until cardiac failure becomes marked. (See Fig. 1A.)

2. The thick-walled, small-lumened pulmonary vessels and high pulmonary vascular resistance present at birth may continue without appreciable change. A balance between the two circulations thus may be maintained which permits sufficient oxygenation of systemic blood for normal activity, yet prevents a high enough pulmonary blood flow to cause cardiac decompensation. Such a balance is theoretically possible but is rarely seen. Signs and symptoms are minimal or absent. (See Fig. 1B.)

3. The thick-walled, small-lumened pulmonary arteries and consequent high pulmonary vascular resistance may continue after birth. Perhaps as a result of this high resistance and consequent pulmonary hypertension, secondary intimal changes may take place, causing a further narrowing of the pulmonary arteries and a further rise in pulmonary vascular resistance. More blood will be directed out the aorta and less through the pulmonary artery. The patient will suffer from increasing anoxia, cyanosis and polycythemia. The patient's symptoms will resemble those of pulmonary stenosis. In actuality, a pulmonary stenosis does exist. In patients with tetralogy of Fallot, the stenosis lies in the outflow tract of the right ventricle. In the conditions under discussion, the stenosis lies in the distal small muscular pulmonary arteries and arterioles. The end result is the same. This sequence of events is classically seen in patients with Eisenmenger complex, in whom cyanosis is absent until about the age of puberty and then becomes progressive. (See Fig. 1C.)

The foregoing considerations have caused the authors to alter their approach to the therapy of this group of congenital malformations of the heart. Wherever possible a direct approach to the malformations should be made, such as closure of a large patent ductus or aortic septal defect. When the direct approach is not feasible, as in instances

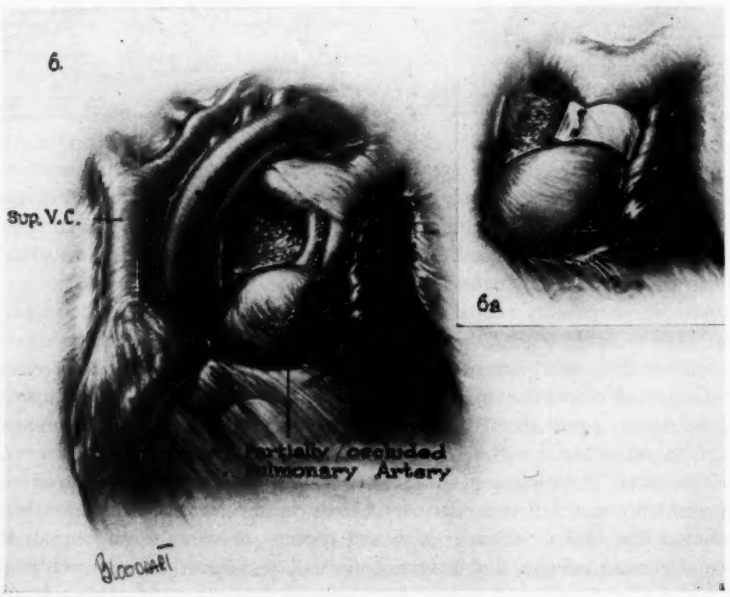

FIG. 2. Drawing demonstrating method of producing pulmonary stenosis. Section of wall of main pulmonary artery has been removed and pulmonary artery is then wrapped with polyethelene film and cotton tape.

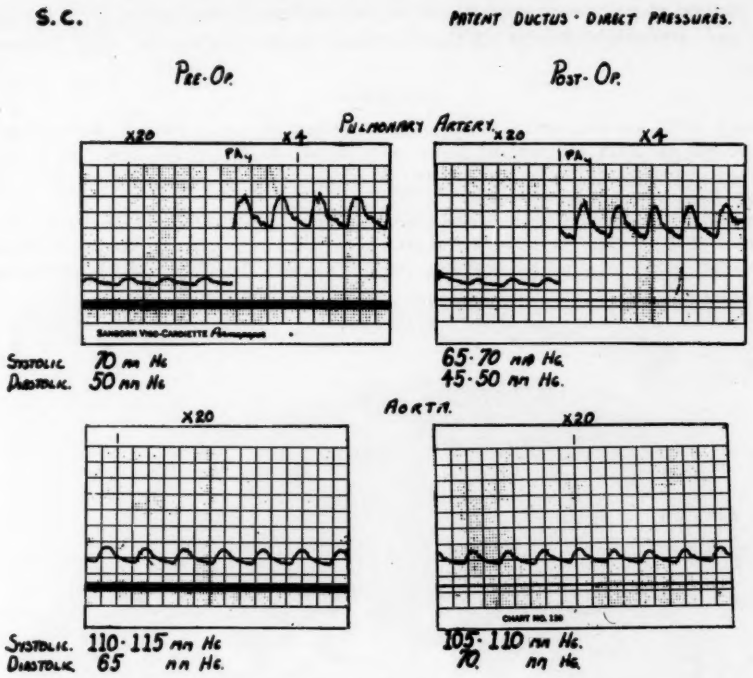

FIG. 3. Direct pressures from pulmonary artery and aorta recorded at surgery from S. C. Note slight fall in systolic pressure and slight rise in diastolic pressure recorded from aorta following closure of ductus.

of single ventricle without pulmonary stenosis, the surgical creation of pulmonary stenosis may effectively reduce the strain on the heart and lungs and return the circulation to a more normal state. The procedure which the authors used to create pulmonary stenosis consists of excision of a segment of wall of the main pulmonary artery and the placement of a band of polyethelene film and cotton tape around the artery. The lumen is reduced in cross sectional area to about 25% of its previous size. (See Fig. 2.)

Creation of pulmonary stenosis has two distinctly different applications. First, in patients in whom the pulmonary vessels are becoming progressively thinner-walled and larger-lumened, with a consequent fall in pulmonary vascular resistance and rise in pulmonary blood flow, the creation of pulmonary stenosis acts to reduce excessive blood flow to the lungs, reduce total cardiac output, and relieve the symptoms of high output cardiac failure. Systemic blood flow and coronary blood flow are increased. Second, in patients in whom the fetal pulmonary vascular bed has been retained and secondary intimal changes of an irreversible nature have begun, the creation of pulmonary stenosis acts to remove the stimulus causing pulmonary artery narrowing thus permitting the pulmonary arteries to progress in a normal manner from thick-walled, small-lumened vessels to thin-walled, large-lumened vessels. The nature of the stimulus is not clearly understood but experimental work in animals and study of autopsy or biopsy material suggest that it is related to arterial pressure and possibly to volume of blood flow as well.

The creation of pulmonary stenosis may be contraindicated when pulmonary resistance is high and irreversible due to advanced intimal changes within the small pulmonary arteries.

Case Reports

Case 1. S. C. was first seen at the age of 6 mo. because of a heart murmur. At that time she weighed 6.8 kg. Birth and neonatal period were normal. At the age of 3 mo. she developed bronchitis. Rapid respirations became constant. Weight gain was poor as compared to her 2 older siblings. There was no history of cyanosis.

On physical examination her color was good; she appeared moderately well developed and well nourished. Blood pressure was 124/50/0 mm.Hg; pulse was 120; respiratory rate was 40. Femoral and brachial pulses were full and bounding. Apex of the heart was felt in the 5th left interspace,

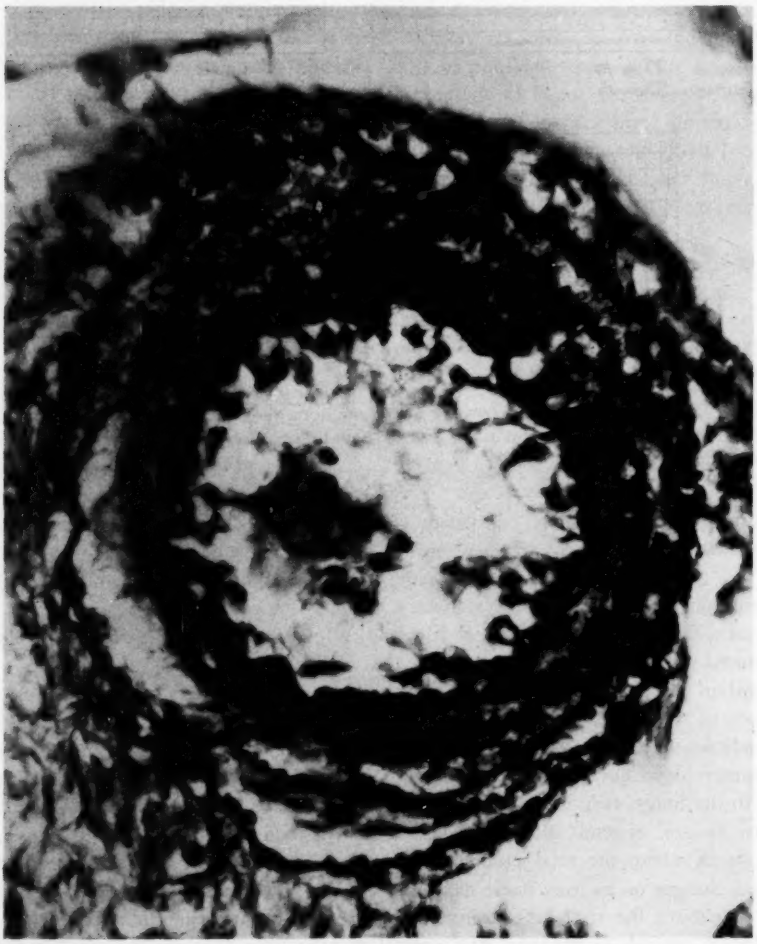

Fig. 4. Small muscular pulmonary artery showing hypertrophy of media and relatively small lumen and normal intima. (Verhoeff's elastic tissue stain and van Gieson's connective tissue stain ×900) Case 1: S. C., 7 mo. old infant with patent ductus arteriosus three-fourths size of aorta. Photomicrographs made by Zane A. Price.

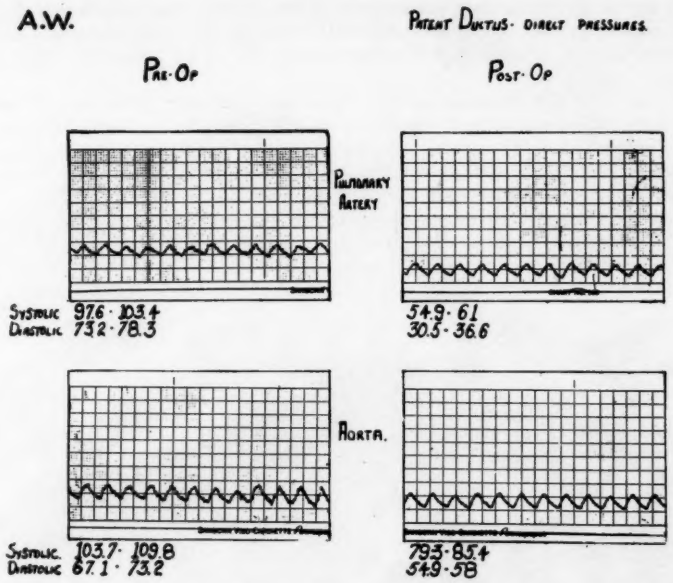

FIG. 5. Direct pressures from pulmonary artery and aorta recorded at surgery from A. W. Note increase in pulse pressure from 36 to 25 in aorta following closure of ductus and marked drop in pressure in pulmonary artery.

almost in the anterior axillary line. Over the heart there was a "confusion of sound." At the base, a loud, long, harsh systolic murmur was present which possibly extended into diastole. Low over the sternum and out toward the apex was a second systolic murmur, lower pitched, not as loud, but rough. In this area, too, there was a long, rough, diastolic murmur. The second heart sound was accentuated and split. Lungs were clear. Liver was 2 cm. below the costal margin.

There was right axis deviation in the ECG. The precordial leads gave evidence of right ventricular hypertrophy and suggested left ventricular hypertrophy as well. On fluoroscopy and roentgen examination the base of the heart was obscured by a large thymus gland. Heart appeared overly active. Lung fields were overly vascular and pulsated actively. Right ventricle was definitely enlarged; the left auricle appeared enlarged.

During the following month her respirations increased and her rate of weight gain decreased. She was brought into the hospital for retrograde aortography. Diodrast injected into the left brachial artery appeared within 1 sec. in the pulmonary vascular bed, probably through a patent ductus. Closure of the ductus was decided upon. At the time of surgery, a large patent ductus, about ¾ the size of the aorta, was found. The pressure in the pulmonary artery (70/50 mm.Hg) was lower than that in the aorta (110/65 mm.Hg). (See Fig. 3.) Pressures in the pulmonary artery were unchanged by closure of the ductus. However, there was a slight fall in aortic systolic pressure and rise in aortic diastolic pressure. Figure 4 represents a typical small pulmonary artery seen on examination of lung biopsy. Patient's postoperative course was uneventful. At the present time, 6 mo. after surgery, she has gained 3.0 kg. in weight, breathes quietly, and is normally active. All murmurs have disappeared. She shows no evidence of cardiac decompensation.

Case 2: A. W., age 13 mo. This little Negro girl appeared perfectly normal at birth but during the first few months of life it was noted that her weight gain was poor, appetite was poor, and breathing at all times was noisy and rapid. She was subject to repeated infections of the upper respiratory tract. She had not had pneumonia. Cyanosis had not been noted.

She appeared small and underdeveloped on physical examination. Respiratory rate was rapid. Blood pressure was 90/0 mm.Hg; pulses were bounding. She weighd 5.3 kg. There was no bulge

of the left side of the chest. Heart was enlarged. A diffuse apical beat was felt over the sternum, suggesting right ventricular enlargement. Maximal in the 2nd left interspace was a loud, long, rough, systolic murmur which seemed to extend slightly into diastole. Chest was clear. Liver was not enlarged.

ECG revealed right axis deviation and left ventricular hypertrophy. There was a suggestion of right ventricular hypertrophy as well. On fluoroscopy the main pulmonary artery segment was full and the lungs appeared overly vascular and active. Left ventricle appeared enlarged, more than the right ventricle. Left auricle was normal. Patient was admitted to the hospital for retrograde aortography. Aortograms revealed rapid filling of the pulmonary vessels after injection of diodrast into the left brachial artery. At the age of 14 mo. she underwent surgery for closure of a large patent ductus arteriosus. Ductus equalled the aorta in size. Pressures in the aorta and the pulmonary artery were essentially the same prior to closure of the ductus, 104/67 and 98/73 mm.Hg, respectively. Following closure of the ductus there was a significant drop in pulmonary artery pressure

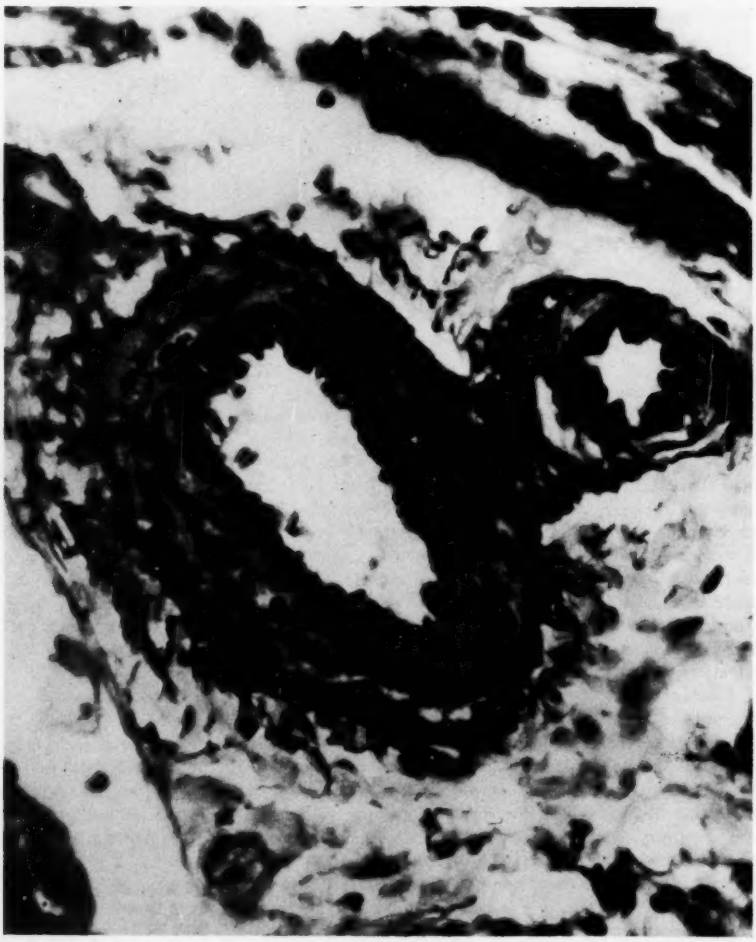

FIG. 6. Small muscular pulmonary artery and arteriole showing medial hypertrophy, small lumen and normal intima. (Verhoeff's elastic tissue stain and van Gieson's connective tissue stain ×900) Case 2: A. W., 13 mo. old infant with patent ductus arteriosus size of aorta.

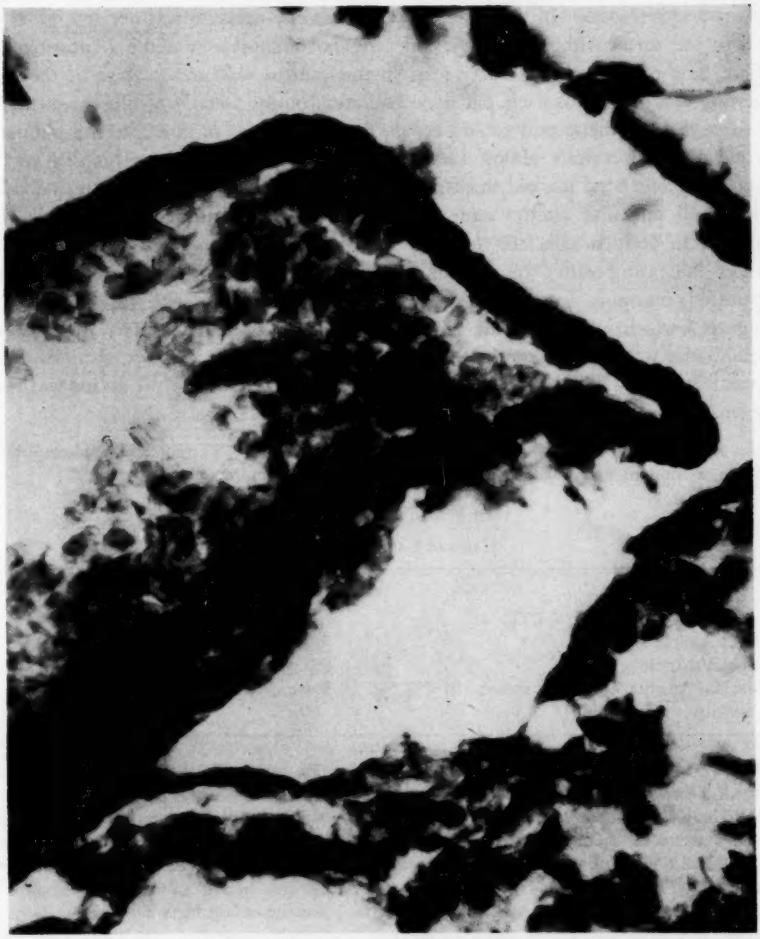

FIG. 7. Small muscular pulmonary artery showing thin media, normal intima and normally wide lumen. (Verhoeff's elastic tissue stain and van Gieson's connective tissue stain ×900) Five year old child with typical small patent ductus and no symptoms.

and a drop in aortic pulse pressure of 12 mm.Hg as shown in figure 5. Figure 6 represents a typical vessel seen on examination of the lung biopsy. Postoperative course was without difficulty. At the present time, 6 mo. after surgery, she is gaining weight well; respirations are slow and quiet. She is active. The systolic murmur has gradually faded but is still faintly heard over the base of the heart. The diastolic murmur, heard for the 1st 4 mo. after surgery, has completely disappeared.

Comment on Case 1 and Case 2

In each patient there was an early onset of symptoms suggestive of cardiac decompensation. The symptoms increased in severity sufficiently to warrant early study and early surgical intervention. At surgery a ductus of large size was found and closed. Pressures taken prior to and following closure of the ductus showed definite evidence of

pulmonary hypertension. In the first patient, pulmonary pressure was not as high as that found in the aorta. Although the authors have not been able to make a consistent correlation, it is of interest that the ductus in this patient was not as large as the aorta, suggesting that the ductus itself put some limitation on the amount of blood which could pass through it. In the second patient the ductus equalled the aorta in size and pulmonary and aortic pressures were almost identical. Examination of the lung biopsies in both instances demonstrated marked thickening of the media and lumens of decreased caliber in the small muscular arteries and arterioles. No intimal changes were noted. These changes were deemed sufficient to cause the elevation of pulmonary pressure. In both instances the postoperative course was excellent. All signs of cardiac decompensation disappeared; murmurs decreased or disappeared. For comparison with Case 1 and Case 2, see figure 7 which is a representative sample of a small pulmonary artery from a 5 year old child who was free of symptoms, had a classical continuous murmur, minimal cardiac enlargement and no evidence of decompensation. At surgery the patent ductus was found to be small.

Case 3: L. B.* This 3½ mo. old infant was referred because of continuously rapid respirations, orthopnea, a constant dry cough, and the presence of a cardiac murmur.

TABLE 1

CARDIAC CATHETERIZATION

L.B.

	O_2 Content (Vol. %)		
Right Auricle	8.2		Assumed O_2 consumption = 50 cc./min.
Right Ventricle	16.0		Pulmonary blood flow = 6.2 l./mm./M^2
Brachial Artery	16.8—Saturation	91.7%	Systemic blood flow = 1.06 l./min./M^2
Capacity	18.3		

On physical examination the baby weighed 3.7 kg. He appeared underdeveloped and undernourished. There was no cyanosis. His breathing was rapid; he was definitely orthopneic. There was a rough, long, loud, systolic murmur maximal in the 3rd and 4th left interspaces, close to the sternum. The second sound at the base was accentuated and split. A diastolic gallop was heard at the apex. Moist rales were heard over both chests. Liver edge was 3 cm. below the right costal margin.

On fluoroscopy and roentgen examination there was definite enlargement of both auricles. The apex was seen extending below the diaphragm in the posterior-anterior projection. Lung fields appeared overly vascular and vigorous pulsations were seen. The main pulmonary artery segment, however, was only slightly convex in the posterior-anterior projection; it became more prominent in the right anterior oblique projection. These findings suggested displacement of the pulmonary artery.

ECG was bizarre and suggested right ventricular hypertrophy. The diagnosis of a single ventricle with a large pulmonary artery arising in an abnormal position was made.

At surgery a large pulmonary artery was found arising to the right of its usual position. The pressure within it was high. The aorta, which lay to the right and posterior to the pulmonary artery, was relatively small. A section of the main pulmonary artery was removed and a band of polyethelene tubing was placed around the pulmonary artery. The cross sectional area of the main pulmonary artery was reduced to about one-third of its previous size. At the time the clamp was placed on the pulmonary artery, cardiac action became stronger and color improved. No lung biopsy was taken. Postoperatively for the first few days there was a delicate balance between cardiac decompensation and compensation. After approximately 20 days, however, the patient began to improve.

* This case was reported in Surg., Gynec. & Obst., August, 1952, except for the postoperative cardiac catheterization which had not been carried out at that time.

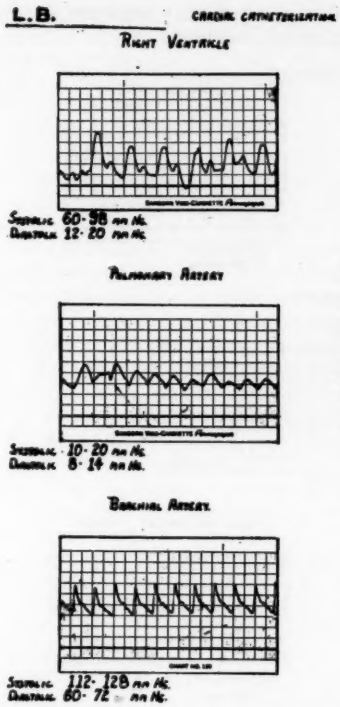

FIG. 8. Pressure recorded from pulmonary artery distal to point of stenosis, ventricle and brachial artery during cardiac catheterization of L. B. Note variations in pressure due to respiration recorded from pulmonary artery. Amplification of pulmonary artery pressure was 5 times that of ventricle and brachial artery pressure.

Weight gain was steady, breathing became quieter, and evidence of decompensation disappeared. At the end of 3 mo. digitalis was discontinued. Improvement continued for an additional 3 mo. and then the rate of weight gain slowed down. He remained active and alert. A trial of digitalis did not improve him. On fluoroscopy, the lung fields still appeared extremely vascular. It was obvious that, although his condition had been benefited by surgery, the patient was still suffering from excessive blood flow to the lungs. In order to establish this fact, cardiac catheterization was attempted. The small size of the infant made catheterization difficult and it was not possible to get all the data desired because of clot formation within the catheter. From the data 2 conclusions can be drawn. First, pulmonary blood flow was excessively high, being about 6 times the systemic blood flow (6.2 l./min./M^2 to 1.06 l./min./M^2). Second, there was strong evidence of pulmonary stenosis, the pressure within the ventricles being 98 to 60/20 to 12 mm.Hg and that in the pulmonary artery distal to the stenosis being 20 to 10/14 to 8 mm.Hg. (See table 1 and Fig. 8.)

Case 4: S. T. This child was first seen at 4½ mo. of age. Birth weight was 3.4 kg.; at 2½ mo. of age he weighed 4.3 kg.; at 4½ mo., 4.6 kg.; at 5½ mo., 4.8 kg. He appeared normal at birth and for the 1st 6 wk. of life did relatively well. Rapid respirations were present shortly after birth; his respiratory rate seemed to increase steadily after the 1st 3 mo. of life. His color had always been good. During the last few weeks prior to admission he appeared constantly irritable and slept poorly.

He appeared undernourished and chronically ill on physical examination. Pulse was 160, respirations 66. His color was pale and there was a suggestion of cyanosis. There was no bulge of the chest. The apex of the heart was felt in the 5th left interspace in the anterior axillary line. A loud, long, harsh, systolic murmur accompanied by a systolic thrill was heard over the entire precordium, maximal in the 3rd left interspace close to the sternum. A diastolic gallop was present at the apex. The second heart sound at the base was accentuated. Rales were heard throughout the chest. Liver was enlarged 4 cm. below the right costal margin. Femoral pulses were normal.

On fluoroscopy and roentgen examination the heart appeared grossly enlarged with enlargement

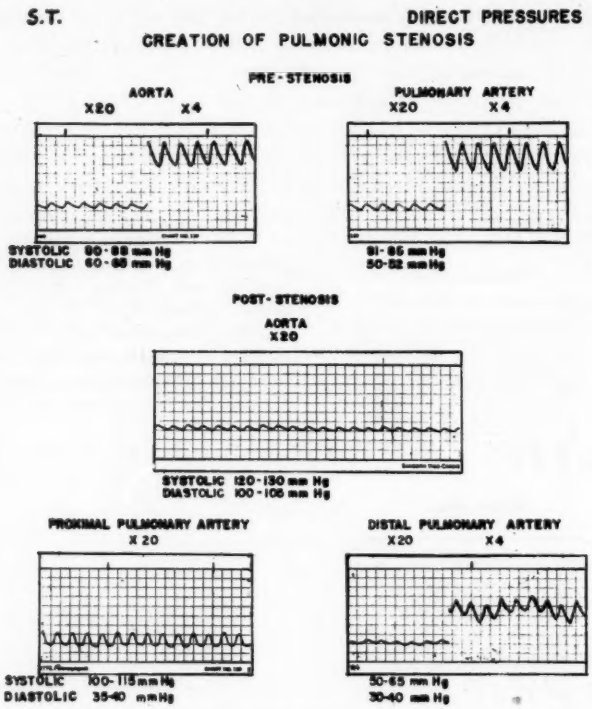

FIG. 9. Direct pressures recorded from aorta and pulmonary artery during surgery from S. T. Note increase in aortic and proximal pulmonary artery pressure following creation of pulmonary stenosis. Note drop in distal pulmonary artery pressure and fall in pulse pressure.

of all chambers. The left auricle displaced the esophagus posteriorly in the right anterior oblique view and to the right in the posterior-anterior projection. The pulmonary artery segment was prominent; the right and left pulmonary arteries were enlarged and pulsated actively. The peripheral lung fields appeared congested.

ECG revealed right axis deviation and right ventricular hypertrophy.

The patient was digitalized and for a short period of time appeared improved. Respiratory rate slowed to 40/min. His color improved, appetite improved and he gained a little weight. However, after about 2 wk. of therapy, signs of cardiac decompensation increased. He was admitted to the hospital for further study.

Retrograde aortography revealed a normally situated aortic arch and descending aorta and failed to reveal evidence of a patent ductus arteriosus or aortic septal defect.

Angiocardiography demonstrated an enlarged right auricle, right ventricle and pulmonary artery. Early in the series of films, a small amount of diodrast was seen in the left ventricle and aorta. Again, late in the series, after visualization of the pulmonary veins and left auricle, the left ventricle, aorta and pulmonary arteries were reopacified. These findings suggested the presence of a large ventricular septal defect. Because of the continuation of cardiac decompensation, the constant presence of rales over both lungs, the rapid respirations and rapid pulse rate, and the large heart and large liver, it was decided to reduce the pulmonary blood flow by the creation of a pulmonary stenosis.

When the chest and pericardium were opened a large pulmonary artery was found arising in its normal position. To the right and posteriorly, a much smaller aorta was seen. Before the pulmonary artery was narrowed, pressures were taken from both the aorta and the pulmonary artery.

The pressure in the aorta was 82 to 84/58 to 59 mm.Hg and that in the main pulmonary artery was 82 to 83/52 to 53 mm.Hg. The pulmonary artery was then narrowed between 75% and 80%. A second series of pressures was taken after this was completed. The pressure in the aorta had risen to 115 to 130/100 to 105 mm.Hg and in the pulmonary artery proximal to the stenosis 105 to 115/35 to 40 mm.Hg. The pressure distal to the stenosis had fallen to 60 to 70/40 to 50 mm.Hg (Fig. 9). Pulse rate decreased from 140 to 120 after the pulmonary artery was constricted. Signs of pulmonary edema cleared completely and heart action appeared much improved. His color remained good. Figure 10 represents a typical muscular artery seen on examination of a lung biopsy.

Case 5: M. F. This 20 mo. old girl appeared normal at birth. Birth weight was 3.3 kg. She weighed 8.2 kg. at the time of admission. On the second day of life a murmur was first heard. Respirations were constantly rapid. Her appetite was poor and weight gain was slow. At no time was cyanosis observed. In the few months prior to surgery the parents and the referring physician noted less activity, poorer food intake and slower weight gain.

She appeared underdeveloped and undernourished without evidence of cyanosis or clubbing on physical examination. Her respiratory rate was 72; blood pressure was 100/70 mm.Hg. There was a marked bulge of the left anterior chest. The apex of the heart was felt in the 5th left intercostal space in the anterior axillary line. There was a precordial heave and a strong pulmonary shock over the base of the heart. There was a long, loud, moderately high pitched, systolic murmur which did not extend into diastole and which was accompanied by a thrill. This murmur was maximal in intensity in the 3rd left intercostal space near the sternum. A mid-diastolic rumble was audible at the apex. The second heart sound was accentuated and split. The lungs were clear, the liver was not enlarged. Pulses in the extremities were equal and normal in quality.

On fluoroscopy there was marked cardiac enlargement. Both ventricles appeared enlarged, the right more than the left. Right auricle was enlarged. There was suggestive enlargement of the left auricle. The main pulmonary artery was markedly enlarged and the right and left pulmonary arteries were large and abnormally active. Peripheral lung fields appeared overly vascular. Roentgenographic examination confirmed these findings.

ECG revealed right axis deviation and right ventricular hypertrophy. Comparison with an ECG taken when the patient was 7 mo. of age demonstrated an increase in the degree of right ventricular hypertrophy and ST-T changes suggestive of right heart strain.

Patient was admitted to the hospital for retrograde aortography and angiocardiography. The aortogram revealed good filling of the arch of the aorta and descending aorta. No diodrast was visualized in the pulmonary arteries. There was no evidence of a patent ductus arteriosus or an aortic septal defect. The angiocardiogram revealed rapid filling of the right side of the heart and pulmonary arteries. In the second film, diodrast was visualized in the left ventricle. Later in the series the pulmonary veins, left auricle, left ventricle and aorta were clearly outlined. At this time there was reopacification of the pulmonary artery.

A diagnosis of a large ventricular septal defect or functional single ventricle with pulmonary hypertension was made. Digitalization was carried out with improvement in appetite but no change in respiratory rate. A thoracotomy was performed and the pulmonary artery was narrowed 75% to 80%. Pressures taken from the aorta and pulmonary artery before and after constriction of the pulmonary artery demonstrated a definite fall in pressure distal to the stenosis of about 15 mm.Hg and a rise in the aortic pressure of about 15 mm.Hg (Fig. 11). Preoperative aortic pressure was 85 to 90/55 and the pulmonary pressure was 60 to 65/35 to 40. Following creation of the stenosis, the aortic pressure was 95 to 105/65. Right ventricle pressure was 100 to 105/5 to 10 and distal pulmonary artery pressure was 46 to 52/26 to 28. Figure 12 represents a typical small artery seen on examination of the lung biopsy.

Case Discussion

These three patients had varying malformations of the heart. One had a single ventricle and two had large ventricular defects. In all three there was evidence of pulmonary hypertension. All three were in difficulty because of excessive pulmonary blood flow. The creation of pulmonary stenosis was beneficial because it reduced the pulmonary blood flow, thus relieving cardiac decompensation. In the first patient, postoperative cardiac catheterization done nine months after surgery suggested that, despite the presence

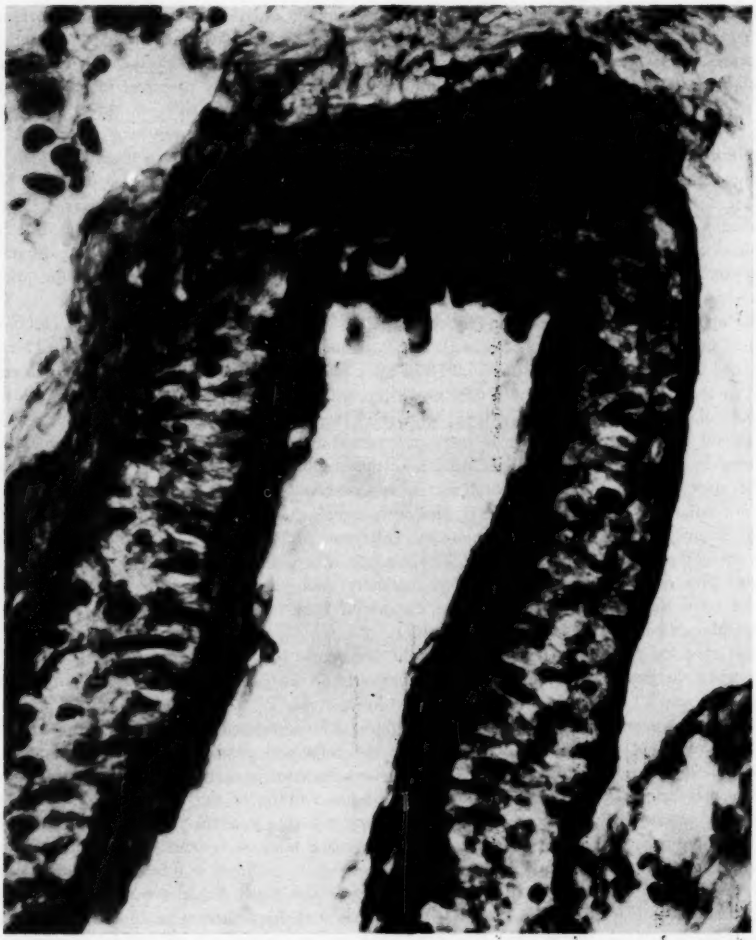

FIG. 10. A (above). Small muscular pulmonary artery (×900). B (opposite page). Arteriole (×1091). Note medial hypertrophy and small lumen. There is also slight intimal thickening of small muscular artery. Case 4: S. T., 6 mo. old infant with large ventricular defect.

of pulmonary stenosis, pulmonary blood flow was still too high. The authors have considered the advisability of reoperation with creation of additional pulmonary stenosis but have delayed doing this, hoping that the present degree of stenosis will prove to be more satisfactory when the patient has grown and developed further.

The immediate effect of creating pulmonary stenosis was well demonstrated in the second and third patients. The rise in aortic pressures following the procedure suggests an increase in systemic blood flow. The difference between the pressures obtained from the proximal pulmonary artery or right ventricle and the distal pulmonary artery demonstrates the presence of a definite stenosis. The fact that the distal pulmonary artery pressure did not fall to normal immediately after the creation of pulmonary stenosis is not a matter of concern. A period of time must elapse before the small-lumened, thick-walled pulmonary arteries seen on examination of the lung biopsy can enlarge

FIG. 10B (see legend on p. 320).

and thin out. In the third patient, the preoperative pressure difference between the aorta and pulmonary artery of 20 to 25 mm.Hg suggests that the volume of shunt through the ventricular defect was limited somewhat by the size of the defect. Following constriction of the pulmonary artery, pressures in the aorta and right ventricle were identical.

The long term value of this surgical procedure cannot yet be analyzed since the first patient (L. B.) was operated upon only 1½ years ago. However, the course to date has been most encouraging. Cardiac failure has cleared. Respiratory rates have returned to normal. Weight gain has improved and physical activity has been normal. Postoperative studies including cardiac catheterization and possibly lung biopsies should be done to determine the effectiveness of the procedure and to establish in each instance whether the degree of stenosis created was sufficient and yet not excessive.

Pulmonary stenosis has been attempted but did not significantly lower the distal pulmonary artery pressure in one older patient with a coarctation of the aorta, ventricular

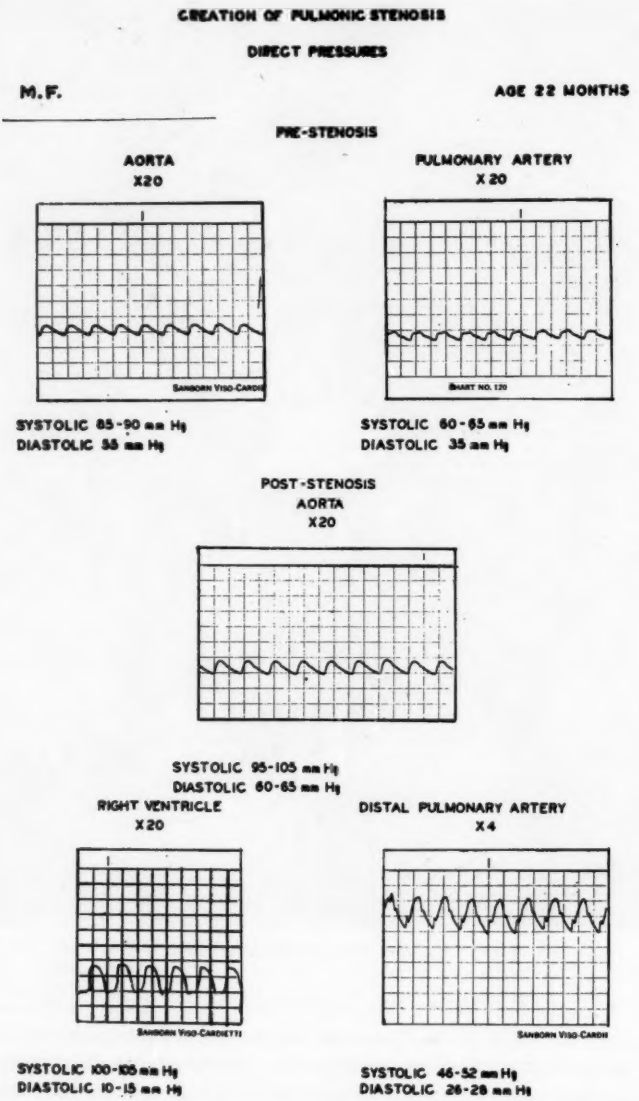

FIG. 11. Direct pressures recorded from aorta, pulmonary artery and right ventricle immediately before and after creation of pulmonary stenosis in M. F. Note fall in pulmonary artery pressure following creation of pulmonary stenosis.

septal defect, a pulmonary artery pressure of 150/60 mm.Hg and a pulmonary artery blood flow that was less than the systemic blood flow because of advanced arterial changes. The pulmonary artery was only narrowed 50 to 60% in that patient. A second attempt is planned for the future in an effort to reverse the pulmonary artery changes and prevent irreversible changes.

FIG. 12. Small muscular pulmonary artery showing medial hypertrophy and luminal narrowing. (Verhoeff's elastic tissue stain and van Gieson's connective tissue stain ×900.) Case 5: 20 mo. old girl with large ventricular defect and excessive pulmonary blood flow.

SUMMARY AND CONCLUSIONS

In the normal human being systemic blood pressure is maintained at a high level by means of the high resistance offered to the flow of blood by the smaller systemic arteries and arterioles. In contrast, pressure in the pulmonary circulation is maintained at a low level because of the relatively large size of the pulmonary vessels. In the fetal and newborn period pulmonary arteries resemble systemic arteries in that they have a small lumen and thick media. In this period pulmonary pressure and resistance are high. As these vessels gradually thin out and enlarge, resistance to pulmonary blood flow falls and consequently pulmonary blood pressure falls.

There is evidence to suggest that the fetal state of thick-walled, thin-lumened pulmonary arteries is retained in instances where the two circulations are joined, such as in patients with a single ventricle, large ventricular defect, aortic septal defect or large

patent ductus arteriosus. As the patient grows, resistance to pulmonary blood flow may: (1) decrease. If the small pulmonary arteries develop normally and become thin-walled and large-lumened, pulmonary resistance will fall. More and more blood will be shunted into the lungs and the patient will develop the signs and symptoms of cardiac decompensation. (2) remain the same. If the small pulmonary arteries retain their fetal characteristics, pulmonary resistance will remain elevated. A balance between systemic and pulmonary blood flow will be maintained compatible with a relatively normal life. (3) increase. If, because of secondary intimal changes, the pulmonary arteries become thicker-walled and smaller-lumened, pulmonary resistance will increase. Progressively less blood will be shunted to the lungs and finally the shunt will reverse and become predominantly venous arterial. The patient will develop the signs and symptoms of pulmonary stenosis with increasing dyspnea and cyanosis.

Data from two groups of patients are presented to illustrate the importance of the pulmonary vascular bed. In the first group, early and severe symptoms of cardiac failure necessitated closure of a large patent ductus arteriosus early in life. The ductus was large, comparable to the size of the aorta, pressures from the aorta and pulmonary artery were similar and a study of the lung biopsies demonstrated that the lumens of the small pulmonary arteries were decreased in size and the media were abnormally thick. In each instance closure of the ductus resulted in a cure.

In the second group the two circulations were joined by either a large ventricular defect or a single ventricle. Three patients were in cardiac failure due to excessive pulmonary blood flow. Pulmonary blood flow was decreased by the creation of pulmonary stenosis, the main pulmonary artery being narrowed 60 to 80%. The postoperative course in these three patients illustrates the value of the creation of pulmonary stenosis in instances where the two circulations are joined by a large communication between the ventricles or great vessels.

Addendum

A second operation was performed in Case 3 (L. B.) and the pulmonary artery narrowed still further. Pressures taken before and after from the pulmonary artery and aorta revealed the presence of a pulmonary stenosis which was increased by the additional constriction of the pulmonary artery. The patient's postoperative course has been excellent suggesting that the degree of pulmonary stenosis present is now adequate.

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SPANISH ABSTRACT

Papel de la Red Pulmonar Vascular en las Enfermedades Congénitas Cardiacas

La presión sanguínea sistémica se mantiene elevada en el sujeto normal gracias a la resistencia ofrecida por las arterias y arteriolas del organismo a la corriente sanguínea. Por el contrario la presión de la circulación pulmonar se mantiene baja debido al tamaño relativamente grande de los vasos pulmonares. En los períodos fetal y del recién nacido las arterias pulmonares se parecen a las del resto del organismo por su pequeña luz y por el gran grosor de sus capas; en estos períodos tanto la presión como la resistencia pulmonar se encuentran elevadas. A medida que se adelgazan y crecen los vasos, disminuye la resistencia a la corriente pulmonar y por lo tanto también la presión sanguínea pulmonar.

Hay hechos que sugieren que se mantiene el estado fetal de paredes gruesas y luz pequeña de las arterias pulmonares en aquellos casos en los que se unen las dos circulaciones, tales como pacientes con ventrículo único, gran defecto interventricular, defecto aórtico y persistencia de un gran conducto arteriovenoso. A medida que crece el paciente, la resistencia a la corriente sanguínea pulmonar puede presentar las siguientes eventualidades:

1. Disminuir.—Si las pequeñas arterias pulmonares se desarrollan normalmente, sus paredes se adelgazan y su luz se amplía, mayor cantidad de sangre se vertirá a los pulmones y el paciente desarrollará los signos y síntomas de la descompensación cardiaca.

2. No ser afectada.—La resistencia pulmonar permanecerá alta cuando las arterias pulmonares conserven sus características fetales. El equilibrio entre la corriente sanguínea sistémica y la pulmonar, mantendrá compatibilidad con una vida relativamente normal.

3. Aumentar.—Así sucederá cuando las arterias pulmonares, debido a cambios íntimos secundarios, engruesan sus paredes y disminuyen su luz; entonces se vertirá progresivamente menor cantidad de sangre a los pulmones hasta invertirse el ritmo de la corriente, que se vuelve predominantemente venoarterial; el paciente desarrolla signos y síntomas de estenosis pulmonar con creciente disnea y cianosis.

Para ilustrar la importancia de la red vascular pulmonar se presentan datos de dos grupos de pacientes. En el primero, los síntomas intensos de insuficiencia cardiaca necesitaron la sutura de un gran conducto arteriovenoso desde época temprana de la vida; el conducto se encontró grande comparable al tamaño de la aorta, las presiones de la aorta y de la arteria pulmonar fueron semejantes y las biopsias pulmonares demostraron que la luz de las pequeñas arterias pulmonares estaban disminuídas, así como la pared enormemente gruesa. En todos los casos, la sutura del conducto produjo curación.

En el segundo grupo se unían las dos circulaciones por un defecto ventricular o bien por la existencia de un ventrículo único. Se encontraron 3 pacientes con insuficiencia cardiaca debida a flujo sanguíneo pulmonar en exceso. La corriente pulmonar se atenuó al crearse una estenosis pulmonar, estrechándose la principal arteria pulmonar de 60 a 80%. La evolución postoperatoria en estos 3 pacientes mostró el valor de la formación de una estenosis pulmonar en aquellos casos en que las dos circulaciones se unen por comunicaciones amplias entre los ventrículos o los grandes vasos.

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HYDROCEPHALUS TREATED BY ARACHNOID-URETEROSTOMY

Report of 50 Cases

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Boston

IT HAS been demonstrated in recent years that a variety of surgical procedures which shunt cerebrospinal fluid away from the subarachnoid spaces are technically feasible and may result in dramatic immediate arrest of progressive hydrocephalus and all of its distressing clinical complications. These surgical procedures include diversion of spinal fluid into the mastoid antrum, into the pleural and peritoneal spaces, into the bone marrow, and into the urinary tract.[1-6] It now seems evident that an objective analysis of longer term results of such operations with respect to growth and development of these children over a period of years is needed—not in any single isolated patient, but in a group of patients treated by a similar technic.

It is the purpose of this paper to report on experiences with 50 consecutive cases of communicating hydrocephalus in which one specific type of shunt, arachnoid-ureterostomy, or diversion of spinal fluid under pressure from the lumbar subarachnoid space to the urinary tract, has been carried out. No attempt is made in this report to compare the results of arachnoid-ureterostomy with those of other procedures but the material presented here becomes available for such comparisons with other experiences. At a later date the results from this clinic of such procedures as third ventriculostomy, ventriculo-cisternostomy, choroid plexectomy, ventriculo-peritoneal shunt, lumbar arachnoid-peritoneal shunt, and ventriculo-pleural shunt will be presented.

OPERATIVE PROCEDURE

Certain principles previously tested in the laboratory in the treatment of experimental hydrocephalus[7] were first applied to a patient with communicating hydrocephalus secondary to diffuse staphylococcus meningitis in 1948. In this patient, a seven year old girl, the left kidney was removed and a small calibre plastic (polyethylene) catheter was used to shunt fluid from the lumbar spinal fluid reservoir into the ureter.[2] The striking success of this procedure in an otherwise desperate situation prompted its early application to the discouraging problem of communicating hydrocephalus in early infancy.

Direct anastomosis of the ureter to the lumbar theca as introduced by Heile in 1925[8] had been tried sporadically in this country and abroad with little success because of its technical difficulties and postoperative complications.[9-11] The operation used in the patients reported here was designed to obviate the complications of direct uretero-arachnoid anastomosis as far as possible. The operation is simple, well tolerated and easy to perform in one stage in patients of any age (three weeks to adult). The operative technic has not varied in this series of 50 children in any essential detail from that previously described.[2]

In all but 2 or 3 instances, the left kidney has been sacrificed simply because it is

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slightly higher than the right and on the aortic side rather than that of the vena cava. The kidney is removed through a standard subcostal incision. Through a separate midline incision the spine and lamina of L_2 are removed exposing an area of dura about 1.5 cm. in length. A short incision is made in the dura in such a fashion as not to open the arachnoid. A pin-point hole only is then made in the protruding arachnoid and the polyethylene tube inserted through it as spinal fluid pours forth. This maneuver insures subarachnoid rather than subdural placement of the plastic tube, which is directed caudally for a distance of about 3 to 4 cm. so that it floats freely among the cords of the cauda equina. The tube is then tunnelled through the paraspinal muscles to the perinephric space and introduced into the ureter for 3 to 5 cm. Three or four silk sutures in the margin of its lumen are used to pull the ureter over the plastic tube and secure it firmly to the fascia of the paraspinal musculature. No ligatures are placed around the ureter at any time and an effort is made to leave its nerve and blood supply intact.

Material

The age distribution of the patients in this series is shown in chart 1. It will be noted that the majority were infants between 3 and 6 mo. of age. In a few instances, hydrocephalus was definitely known to be a sequel to generalized bacterial meningitis. In most of these patients, however, there were no clues in the history to suggest the etiology of the communicating hydrocephalus determined

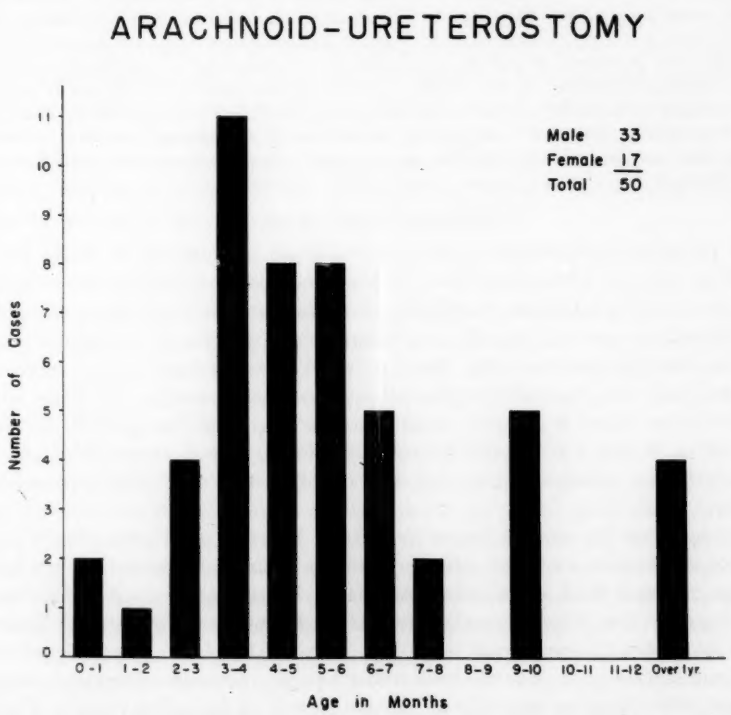

Chart 1. Age and sex distribution of 50 children in whom arachnoid-ureterostomy was performed in treatment of communicating hydrocephalus. No patients have been omitted from this series except those in whom procedure was carried out as palliative measure to relieve hydrocephalus incident to inoperable tumor.

by the preoperative studies. A number of additional patients who have had arachnoid-ureterostomy performed as a palliative procedure to relieve pressure associated with inoperable tumors are not included in this report.

Preoperative studies include those necessary to establish the diagnosis of progressive communicating hydrocephalus as well as urine analyses, nonprotein nitrogen determination and intravenous urography to insure the presence of 2 normally functioning, uninfected kidneys. Communicating hydrocephalus is established by combined ventricular and lumbar puncture with hydrodynamic, tracer dye and air studies. The extent of the hydrocephalus is determined by ventricular air-bubble studies.[13]

Arachnoid-ureterostomy has been performed only in children with a severe degree of hydrocephalus and only in children in whom it has been established that the hydrocephalus is progressive; that is, in patients in whom the head size is steadily increasing at an accelerated rate and in whom the rate of absorption and excretion of a tracer dye (phenolsulphonephthalein) placed in the subarachnoid space is markedly diminished. In this series of 50 patients, the tracer dye passed from the lateral ventricle to the subarachnoid space in 4 patients in less than 2 minutes, in 15 patients in between 2 and 4 minutes, in 19 patients in between 4 and 10 minutes, and in 7 patients in between 10 and 20 minutes; in 4 patients the test was not done or was unsatisfactory. The 12 hr. urinary excretion of the dye injected into the ventricle was less than 10% in 7 patients, from 10 to 20% in 29 patients and from 20 to 30% in 7 patients; normal excretion over a 12 hr. period with satisfactory urinary output should be 45 to 80%.

Many patients have been considered for surgery and regarded as unsuitable because ventricular air studies revealed the cortex compressed to a thickness of only a few millimeters, or because the baby appeared to be blind or otherwise irreversibly damaged. Among this series of 50 patients the cerebral cortex measured less than 1 cm. in thickness from the lateral ventricle to the surface in 12, between 1 and 2 cm. in 23, between 2 and 3 cm. in 14 and greater than 3 cm. in only 1 patient.

An effort has been made to evaluate each infant with hydrocephalus individually on the basis of all the information available and not on any single test; if there seemed to be reasonable possibility that with arrest of the hydrocephalus normal development might proceed, operation has been recommended. As will be pointed out subsequently, in only one of the surviving patients is it now felt that the baby was irreversibly damaged too severely prior to operation to permit a satisfactory result. It was, therefore, poor clinical judgment to operate on this patient.

Postoperative Course

The immediate postoperative course after arachnoid ureterostomy is usually smooth. Parenteral fluids are administered for 2 or 3 days routinely and subsequently only if the intake by mouth is inadequate. Ordinarily by the fourth or fifth postoperative day these infants exhibit a ravenous appetite and feedings must be repeatedly increased to keep them satisfied. At about this time also, it is noted that they become much more alert, smile and play, and lose their preoperative hyperirritability, disorganized motor activity and restlessness. There is transient rise in the blood nonprotein nitrogen level, usually to about 40 to 60 mg./100 cc. This returns to normal in 2 to 3 weeks and presumably indicates that the remaining kidney has satisfactorily met the additional burdens placed upon it.

After operation the anterior fontanelle remains depressed at all times (Fig. 1). If it does not do so, even when the infant is crying, it undoubtedly means that satisfactory drainage of spinal fluid is not taking place. The cranial bones overlap one another to some degree so that ridges appear at the sites of the sutures. In infants, the head size usually diminishes in circumference by 1.0 cm. up to as much as 4.0 cm. depending upon the degree and rapidity of onset of the hydrocephalus prior to operation. From approximately two weeks after operation on, the head does not grow at all for a period usually of one to two years. At this time, or presumably whenever the infant's body size has caught up to proper proportion to the head size, the circumference of the head again begins to increase, but now at a normal rate.

In those patients who have had lumbar or ventricular taps performed after surgery

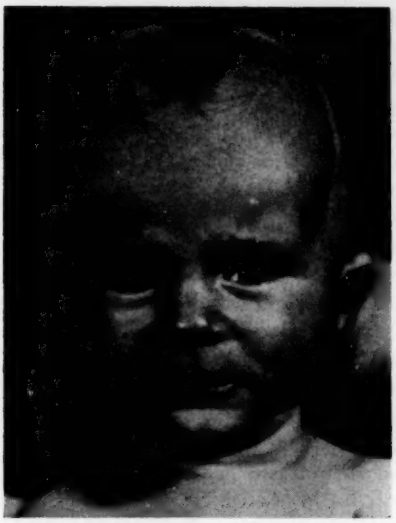

FIG. 1. Infant 3½ mo. of age after arachnoid-ureterostomy showing persistent depression of anterior fontanelle and overlapping of the frontal and parietal bones at coronal suture line. Head became 2 cm. smaller in circumference after operation.

while the shunt was in satisfactory operation, the cerebrospinal fluid pressure has been from 50 to 90 mm. water. No sequelae of significance have been noted from this persistent intracranial hypotension. Three or four patients have had subsequent ventricular air studies for one reason or another and have shown a marked decrease in the size of the ventricular system. This has also been noted at postmortem examination in patients who have died a number of months after operation because of acute dehydration. It suggests, of course, that much of the thinning of the cerebral cortex is due to compression of interstitial fluid out of the brain by the expanding ventricles.

RESULTS

In this series there has been only one death during the postoperative period. This was a three months old infant in extremely poor general condition who developed postoperative aspiration pneumonitis and died suddenly from recurrent aspiration on the seventh day after operation. There have been no other deaths during the hospitalization in which the initial surgical treatment was carried out.

There have been no technical problems with establishment of a well functioning shunt at the initial operation with one exception. This was in a 2½ week old, 3.0 kg. infant in whom the ureter was too small to receive the smallest size polyethylene catheter available. In two other infants, each 4 weeks of age and weighing about 3.2 kg., a small size catheter (internal diameter equal to a #19 intravenous needle) was satisfactory. In six patients obstruction developed in the shunt from 5 to 14 months following operation. These patients were all re-explored and in every case there was found to be a block in the tip of the tube within the subarachnoid space; this was apparently a plug of fibrin, arachnoid, or perhaps an adherent nerve root. In each of these six patients a new tube was inserted and has functioned satisfactorily for periods varying from 1 to 31 months to date. In no instance, either clinically or in patients examined at post mortem, has there been any demonstrable obstruction or reaction at the ureteral end of the plastic tube.

There has been no obstruction of the arachnoid-ureterostomy as a result of growth alone up to four years after operation, as far as is known. Since both the ureter and the

structures within the spinal canal grow with the child and since there is 4 cm. of the plastic tube introduced into both the ureter and the spinal subarachnoid space, it is not anticipated that growth will ever in itself obstruct this type of shunt.

There has been no infection of either the nephrectomy or the laminectomy wounds in any of these patients. There has been early postoperative meningitis in two patients, in both due to B. coli. Both patients eventually succumbed after lingering illness of 4 and 6 months in spite of all antibiotic treatment and the persistent patency of the shunt. In only one of these was B. coli also cultured from the urine. Two other patients in this series died because of central nervous system infection. One was a child operated on ill-advisedly, early in the series, who had apparently an active ependymitis at the time and died two months after operation with an aqueduct block and extensive ventriculitis but never a positive spinal fluid culture. The other was a patient with salmonella meningitis, who was operated upon for hydrocephalus after the spinal fluid had been sterilized. The patient did well but remained a salmonella carrier in her intestinal tract and died of virulent recurrence of salmonella ventriculitis and meningitis eight months after arachnoid-ureterostomy. Five additional patients at various periods several months after operation have had fever, stiff neck, irritability and an increased number of white blood corpuscles in the spinal fluid. One of these only had a positive culture (B. proteus). These patients have all responded well to supportive and antibiotic therapy.

The most difficult problem postoperatively with these patients has been the control of their electrolyte and water balance during periods of intercurrent illness. As long as these children have been in good health, afebrile, maintaining a normal intake of food and fluids, and not vomiting or having diarrhea, there has been no problem in dehydration. However, eight infants, and perhaps one or two more, have died at periods from 3 weeks to 12 months after operation of acute overwhelming dehydration secondary to some variety of intercurrent illness, usually an upper respiratory or gastrointestinal infection.

The reasons for this bear some explanation. They are evident on the basis of metabolic balance studies done at the Children's Medical Center under the direction of Dr. William Wallace. These studies were carried out in hydrocephalic infants before and after arachnoid-ureterostomy. The infants were placed on a virtually sodium-free diet but with a normal total fluid intake. On this diet, since the kidneys conserve sodium, a constant low level of sodium is reached in the urine within a few hours. Dehydration and weight loss do not occur. After arachnoid-ureterostomy, balance studies in the same patients were carried out on the same sodium-free diet and fluid intake. Although the remaining normal kidney continues to do its job of conserving sodium and fluid, there is now in the voided urine a quantity of spinal fluid from the shunt containing sodium and chloride at normal spinal fluid levels. If this loss of fluid and electrolytes is not replaced by adequate intake, the defence of normal plasma volume by transfer of interstitial fluid into the vascular system fails and may do so quite abruptly. The result may be profound peripheral vascular collapse and death in a clinical picture resembling that of an Addisonian or hypoadrenal crisis. A summary of one of these metabolic studies is charted in chart 2.

The clinical implications of these balance studies are obvious. In young infants, when the diet consists largely of cow's milk, the sodium intake is low, in the neighborhood of only 1 to 2 gm. per day. The amount of sodium lost in the spinal fluid after arachnoid-ureterostomy in such an infant may represent, therefore, a significant fraction of the total

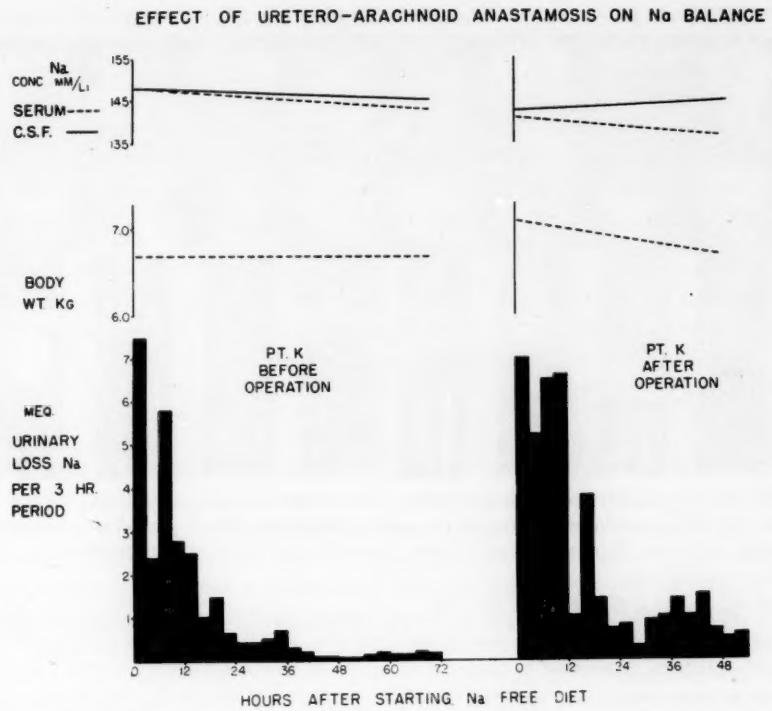

CHART 2. Metabolic balance chart on hydrocephalic infant placed on sodium-free diet before and after arachnoid-ureterostomy. On left (before operation) urinary excretion of Na drops to negligible amount, body weight does not change, and there is little change in serum Na concentration. On right (after operation) there is continued excretion of Na, body weight falls off sharply and serum concentration of Na diminishes; experiment was discontinued after 50 hr. because of patient's alarming clinical appearance.

intake. In other words, an infant on a milk diet is on the verge of negative sodium and fluid balance at all times if he is losing 150 to 250 cc. of spinal fluid daily. If then, such an infant develops an infection, vomits frequently, has diarrhea, or does not maintain a normal fluid and salt intake, acute dehydration accompanied by weight loss and profound shock may ensue. If treated soon enough, balance can be restored easily by intravenous infusion of fluids and salt.

In an attempt to obviate the danger of acute dehydration, all of these infants are placed on 2 gm. (½ teaspoon) of ordinary table salt per 24 hours after operation and this is continued indefinitely. This is given prophylactically even though it is not actually necessary as long as the child is in good health and eating and drinking well. In addition, all these infants should be offered extra fluids beyond that given with the regular formula. Much more important than the prophylactic use of salt and extra fluids, however, is the realization that critical dehydration may occur within a very few hours when one of these patients becomes ill and refuses his normal fluid intake, particularly if there is vomiting in addition. This problem is discussed with each patient's parents and with the pediatrician before the infant leaves the hospital. Parenteral fluids and salt should be

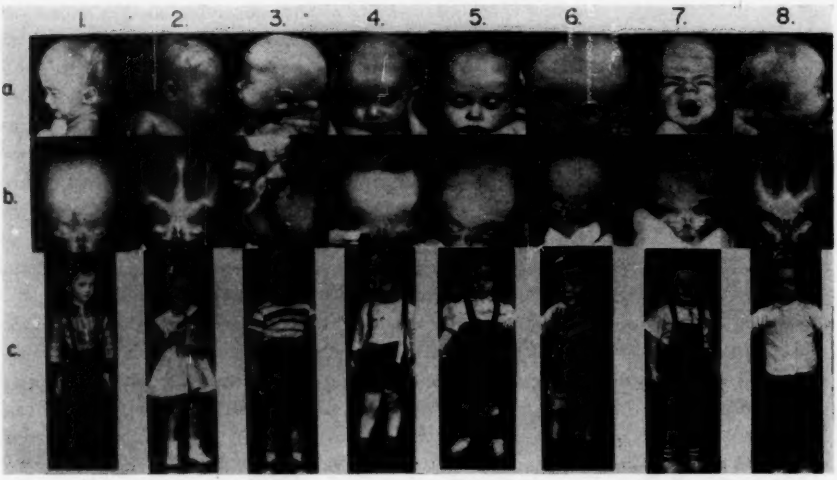

FIG. 2. Hydrocephalic infants followed from 2 to 4 yr. after arachnoid-ureterostomy. In following legends, (a) refers in each patient to preoperative photograph, (b) to preoperative ventricular air-bubble study and (c) to appearance of infant at period more than 2 yr. after operation.

1. (a) 5 mo. old male.
   (b) AP upright ventricular air-bubble study.
   (c) 3 6/12 yr. postoperative (now 4 3/12 yr. postoperative); normal intelligence, negative neurologic examination.
2. (a) 4 mo. old female.
   (b) AP brow-up ventricular air-bubble study.
   (c) 3 3/12 yr. postoperative (now 3 9/12 yr. postoperative); normal intelligence, negative neurologic examination.
3. (a) 4 mo. old male.
   (b) Lateral upside-down ventricular air-bubble study.
   (c) 3 yr. postoperative (now 3 5/12 yr. postoperative); normal intelligence, negative neurologic examination.
4. (a) 2½ mo. old male.
   (b) AP upright ventricular air-bubble study.
   (c) 2 yr. postoperative (now 3 yr. postoperative); normal intelligence, negative neurologic examination.
5. (a) 5 mo. old female.
   (b) AP upright ventricular air-bubble study.
   (c) 2 6/12 yr. postoperative (now 3 yr. postoperative); probable slight mental retardation, mild left hemiplegia.
6. (a) 7 mo. old male.
   (b) AP upright ventricular air-bubble study.
   (c) 1 5/12 yr. postoperative (now 2 8/12 yr. postoperative); normal intelligence, negative neurologic examination.
7. (a) 1 mo. old male.
   (b) AP upright ventricular air-bubble study.
   (c) 2 2/12 yr. postoperative (now 2 7/12 yr. postoperative); probable normal intelligence; bilateral unsustained ankle clonus only positive neurologic finding.
8. (a) 2½ mo. old female.
   (b) AP brow-up ventricular air-bubble study.
   (c) 2 6/12 yr. postoperative; normal intelligence, coordination poor but improving.

given at once to any postoperative patient who vomits more than once or twice or fails to drink or appears at all dehydrated on examination of the skin and mucous membranes or estimation of the urine output.

As previously stated, at least 8 patients in this series, and perhaps 9 or 10, have died in this syndrome of acute dehydration secondary to infection. The first two died before the problem could be realized and the others in spite of efforts to impress on the family the seriousness of minor infections in these infants. In reviewing the deaths in those cases in which adequate information is available, it is felt that a fatality might have been avoided by earlier recognition and more vigorous treatment of the fluid balance problem in every instance. In an acute crisis, normal saline and one-half molar sodium lactate solution given intravenously rapidly is recommended. A vein should be exposed and cannulated if necessary since fluid and electrolytes cannot be replaced quickly enough by mouth or by subcutaneous administration in severe dehydration of rapid onset.

There will probably always be an irreducible minimum of critical situations where such a baby is in an isolated community or the family simply cannot be made to understand and cooperate; however, with intelligent, alert parents and astute pediatric care, it should be possible to avoid this complication in almost every instance.

To turn now to a pleasanter and more gratifying aspect of this report. Of the 50 children in this series, 33 are living. The encouraging feature to this author, however, is not that 33 out of 50 children with this severe degree of hydrocephalus are still alive, but that of these 33 only one is grossly retarded to the point of needing institutional care. Five other patients are definitely retarded behind a normal developmental schedule but are happy, asymptomatic children at home making progress. The most interesting feature of all is that 24 of the group are known to be in excellent health with normal or close to normal mental and motor development at periods ranging from a few months to over four years from operation. Three additional patients have not been followed long enough to be at all certain about. So that of the 33 living patients at the present time, 29, and perhaps as many as 31, can be classified as satisfactory to excellent results. On the basis of previous clinical experience, these are all children in whom the degree and rate of progression of hydrocephalus were such that, with the occasional unexplainable exception, they would have been dead or severely retarded with markedly enlarged heads if surgical treatment had not been carried out.

Thirty patients in this series have been followed longer than two years. Twenty of these are alive and as already implied, all but one doing well. A group of these is shown in figure 2, together with their preoperative photographs and ventricular air-bubble studies. This illustrates perhaps better than any verbal description that normal appearance and progressive development is possible with severe degrees of hydrocephalus in early infancy if definitive treatment is accomplished early enough.

Summary

Parents of an infant with hydrocephalus are interested not in having their child kept alive but in giving it a chance for normal development. Therefore, once it is established that progressive hydrocephalus exists, temporizing measures and prolonged observation should be discouraged in favor of a definitive procedure which will immediately and continuously reduce spinal fluid pressure to within normal limits. This series of patients indicates that this objective can be accomplished by diversion of cerebrospinal fluid into the urinary tract. The complications of this procedure are three: (1) mechanical obstruction of the shunt, which has been seen in only a few cases and has always been remedi-

able; (2) meningitis, which has occurred in 8 out of 50 patients postoperatively and has been fatal in 3; and (3) acute dehydration secondary to intercurrent infection because of unreplaced loss of fluid and electrolytes through the shunt, which has been fatal in 8 to 10 of these patients.

Thirty-three out of 50 patients with severe communicating hydrocephalus treated by arachnoid-ureterostomy are living, and of these 31 are satisfactory to excellent results to date.* At least 24 of these children appear to be entirely asymptomatic with normal or close to normal mental and physical development at periods from a few months to over four years.

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Spanish Abstract

Hidrocefalia Tratada por la Aracnoides-Ureterostomía

No es la vida del niño sino su desarrollo normal lo que interesa a los padres de un niño con hidrocefalia. Por lo tanto no debe realizarse una observación prolongada o practicarse métodos contemporizadores una vez que se ha establecido el diagnóstico de hidrocefalia progresiva, y sí decidirse por un procedimiento definido que reduzca inmediata y continuamente la presión céfalo-raquídea a límites normales. Los pacientes de esta serie señalan que puede realizarse este objetivo al derivar el líquido céfalo raquídeo a las vías urinarias.

Las complicaciones de este procedimiento son tres:

1. Obstrucción mecánica de la derivación, observada en pocos casos y que siempre ha sido remediable;
2. Meningitis, que se ha presentado en 8 de los 50 casos en el período postoperatorio, habiendo sido fatal en 3;
3. Deshidratación aguda secundaria a infección intercurrente por no haberse restituído la pérdida de líquidos y electrolitos por la derivación, lo que ha sido fatal en 8 de 10 pacientes.

Actualmente viven 33 de los 50 pacientes y de ellos 31 tienen resultados desde satisfactorios hasta excelentes; los 50 casos presentaban hidrocefalia comunicante intensa y todos fueron tratados con la aracnoides-ureterostomía. 24 de los 31 niños con resultados satisfactorios se encuentran completamente asintomáticos, con desarrollo mental y físico normal o casi normal, en el período de observación postoperatorio de unos cuantos meses a más de cuatro años.

300 Longwood Avenue

* This series has been extended to 64 patients, of whom 45 are living and 42 are satisfactory results to date.

Pediatrics

VOLUME 12 SEPTEMBER 1953 NUMBER 3, PART I

SPECIAL SECTIONS

NEWS AND ANNOUNCEMENTS

The American Pediatric Society held its 63rd annual meeting on May 6-8, 1953, at the Hotel Traymore, Atlantic City. The following members were elected as officers for the year 1953-54:

President, Dr. Rustin McIntosh; Vice President, Wilburt C. Davison; Secretary-Treasurer, Aims C. McGuinness; Recorder-Editor, Stewart H. Clifford. Member of the Council (7 years), John A. Anderson.

The following candidates were elected to active membership in the society: Drs. Neva M. Abelson, Philadelphia; Janet S. Baldwin, New York; William Berenberg, Boston; A. L. Chute, Toronto; Clifford G. Grulee, Jr., New Orleans; Janet Hardy, Baltimore; Chris P. Katsampes, Rochester; John D. Keith, Toronto; John A. Lichty, Denver; Edmund R. McCluskey, Pittsburgh; Robert J. McKay, Jr., Burlington, Vt.; Lawrence B. Slobody, New York; Alexander J. Steigman, Louisville; Lewis Thomas, Minneapolis; Richard Wagner, Boston.

* * *

Deaths of the following members during the past year were announced: Drs. Clausen, Dorning, Jeans, Knox, Klaus, Van Ingen.

Dr. Grover F. Powers, New Haven, was awarded the second annual John Howland medal. This was presented for the society by Dr. Daniel C. Darrow, New Haven.

The Society will meet at Buck Hill Falls, Pa., May 6 to 8, 1954, and at the Chateau Frontenac, Quebec, in June 1955.

* * *

The Society for Pediatric Research held its 23rd annual meeting in Atlantic City, May 4 to 6, 1953. Dr. Robert Ward, New York, presided. The following officers were elected for 1954: President, Dr. Harold Harrison, Baltimore; Vice President, Dr. Russell Blattner, Houston; Secretary-Treasurer, Dr. Sydney S. Gellis, Boston; Members of Council, Dr. Charles Lowe, Buffalo, and Dr. C. Henry Kempe, San Francisco.

* * *

The Endocrine Society and the University of Minnesota announce a Postgraduate Assembly in Endocrinology and Metabolism for Physicians, the Sixth Annual Assembly sponsored by The Endocrine Society, which will be presented on the University of Minnesota campus from Sept. 28 to Oct. 3, 1953.

All aspects of clinical endocrinology and metabolism will be taken up, and recent important advances in the field will be stressed. Informative demonstrations and illustrative clinical cases will be presented, and 10 panel discussions will provide registrants with opportunities to bring up special problems and questions.

Faculty for the Assembly includes outstanding authorities in the field of endocrinology from various

parts of the country as well as members of the faculty of the University of Minnesota Medical School and the Mayo Foundation. The program will be presented under the direction of Dr. Edward C. Reifenstein, Jr., General Chairman for The Endocrine Society, and Dr. C. J. Watson, Professor and Head, Department of Medicine. Chairman of Local Arrangements on behalf of the Endocrine Society is Dr. Edmund B. Flink. For further information write to the Department of Continuation Study.

* * *

Dr. Albert B. Sabin, Cincinnati, has been elected an active member in the Association of American Physicians at its annual meeting in Atlantic City, May 6, 1953. Dr. Sabin is a member also of the American Pediatric Society. He is best known for his contributions in the field of viral diseases.

* * *

Dr. Glidden L. Brooks, Pittsburgh, has been appointed as the first full-time Medical Director for United Cerebral Palsy. He has been serving as Professor of Hospital Administration in the Graduate School of Public Health and Associate Professor of Pediatrics in the School of Medicine, University of Pittsburgh.

* * *

A portrait of Dr. F. Tom Mitchell, Professor of Pediatrics, University of Tennessee, and Chief of Staff of the Le Bonheur Children's Hospital, was presented to the University of Tennessee on June 11, 1953, in honor of his many years of service in the division of pediatrics. The portrait was hung in the conference room of the Le Bonheur Children's Hospital, Memphis.

BOOK REVIEWS

GENETIC NEUROLOGY, edited by Paul Weiss, Chicago, University of Chicago Press, 1951, $5.00, 239 pp.

The term "genetic neurology" describes a new biologic discipline defined as the study of all processes involved in the maturation of the nervous system, the maintenance of its integrity and the process of restoration after disruption. This volume summarizes the symposium held in March 1949, in Chicago, and subsidized by UNESCO, at which this new discipline was literally born. It includes papers by 19 of the outstanding authorities in all phases of the study of the physiology, biochemistry, embryology, pathology, etc., of the nervous system.

It is highly technical in its respective fields. As an authoritive statement of present concepts of some aspects of neuro-embryology, nerve regeneration, neuro-biochemistry, nerve differentiation, and many associated aspects, it should prove of value to research workers in these fields. Its value for pediatricians, practicing, academic or otherwise, will be extremely limited.

EL PREMATURO, José Obes Polleri, Montevideo, Uruguay, García Morales-Mercant S.A., 1952, 273 pp.

This monograph presents the author's views on the present-day status of the problem of prematurity, its related pathology and desirable methods of care. The author has compiled a truly exhaustive bibliography and appears to have included almost everything which has appeared in the North and South American and European literature on this subject in recent years. References to the published material, however, are not always critical.

Care of the uncomplicated, as well as the complicated cases of prematurity, is discussed in considerable detail. After an extensive examination of the relative merits of human and other forms of milk in feeding, in which the author reports his own results as indicating no essential differences, he still states his preference for human milk as a base. Modification, however, through addition of supplements, he considers essential.

The approach is predominantly clinical and statistical and it is unfortunate that the author has not amplified the problems of public organizations of care for the premature infant. Particularly where medical and hospital resources are as limited as in Latin America, a broad public health program, aimed at both prevention of prematurity and the most adequate care possible for all premature infants, is essential.

In view of its extensive clinical coverage, the book is an important addition to the Spanish literature on prematurity.

ELECTROENCEPHALOGRAPHY IN CLINICAL PRACTICE, Robert S. Schwab, Philadelphia, W. B. Saunders Company, 1951.

In a compact yet clear manner, this book discusses the uses and limitations of encephalography in the diagnosis, study and treatment of diseases of the central nervous system. Technical details, controversial matter, and interpretative record evaluations are offered in as simplified a manner as is possible, and consistent with reasonable accuracy.

In addition to short descriptions of the pertinent historical background, basic neurophysiology involved and general technics, the book also includes chapters on the relationship of the EEG to epilepsy, neurologic and neurosurgical problems, and psychiatric conditions. The choice of representative cases and records and methods of descriptions and implications are effective.

The book should prove valuable as an introductory volume for those practicing physicians of all the specialties whose contact with the subject of electroencephalography has been only of the most superficial and who feel the need of more background knowledge for the proper use and interpretation of what the EEG can offer in the care of their patients.

SYMPOSIUM ON CARBOHYDRATE METABOLISM, Third M & R Pediatric Research Conference, Nov. 16, 1951, revised and re-issued, Columbus, Ohio, M & R Laboratories, 1952.

The pediatrician will find a precise presentation of much valuable information on the physiologic, biochemical and clinical aspects of carbohydrate metabolism. Enzymatic synthesis and degradation of glycogen and the influence of hormones on carbohydrate metabolism and electrolyte balance are discussed by Drs. Carl F. Cori, Earl W. Sutherland, C. R. Park, A. Baird Hastings and Evan Calkins. The clinical application of these physiologic and biochemical aspects to glycogen storage disease, hypoglycemia and diabetic acidosis are discussed by Drs. Dorothy H. Andersen, Irvine McQuarrie and Allan M. Butler. Dr. Victor Najjar should be congratulated for the manner in which he has condensed the content of the original papers to produce a report which provides so much physiologic information in a form so palatable to clinicians.

ON THE BRINGING UP OF CHILDREN, Susan Isaacs, Ella Freeman Sharpe, Melanie Klein, Merell P. Middlemore, and Nina Searl, edited by John Rickman, Brunner, 1952, $3.00, 243 pp.

This small book is a new edition of a popular volume first printed in 1936. It consists of 6 essays written by well known British psychoanalysts. Four of the contributors have died since publication. The best known are John Rickman, who was a distinguished psychiatrist, and who was responsible for editing this book, and Susan Isaacs, a well known educator and researcher in child development.

The aim of the authors was that of preventing behavior problems and neuroses through helping parents rear their children in a more healthy fashion psychologically. The chapters are titled "Planning for Stability," "Weaning," "The Uses of Sensuality," "Questions and Answers," "Habit" and "The Nursery as a Community." In them, one finds a good mixture of theories of personality development and practical suggestions for child rearing. Tucked away in each essay is discussion of such common clinical problems as thumb-sucking, night terrors, sex play and aggressive acting out. There are no chapter subheadings, nor an index, to identify these and other topics. This leaves the reader no choice but to read along, sooner or later coming to those items which concern him particularly. However, the material is so well written and so interesting that one is easily motivated to read a section to completion.

PSYCHIATRY AND MEDICAL EDUCATION, American Psychiatric Association, Washington, D.C., 1952.

This is a report of the 1951 Conference on Psychiatric Education, held at Cornell University in June, 1951, organized and conducted jointly by the American Psychiatric Association and the Association of American Medical Colleges.

Participants included pediatricians, along with educators in other disciplines, who attempted to define the role of psychiatry in medical education. "Psychiatry" was considered in a broad sense; teaching of emotional growth and development and of behavior in infancy and childhood was included within its framework.

The Conference marked a landmark in the assessment of medical education. Groups of participants met frequently for many months in preparation of the meeting, and in the collection of resource material. The Conference report includes a rich bibliography, collected by the preparatory commissions, but the main portion of the monograph consists of an interpretation of the purpose of the Conference, its accomplishments and a summary of current practices and proposed changes. Teachers of pediatrics will find this book valuable since it describes content and methods of undergraduate medical education, with emphasis on the teaching of medical psychology. Suggestions for enriching pediatric education with a closer tie to psychiatry and the social sciences will result from careful reading of this document.

In Memoriam

PHILIP VAN INGEN
1875 — 1953

IT IS with a deep sense of loss that we record the passing of Philip Van Ingen on March 28, 1953. The children of America are in his debt for the great contributions to their welfare which he made in his lifetime.

After a boyhood in New York, he attended Hill School at Pottstown, Pa., and after graduation there went on to Yale University to receive an A.B. degree in 1897. He received his M.D. degree from the College of Physicians and Surgons, Columbia University, in 1901. He served a two-year internship at the Presbyterian Hospital in New York City and a residency in pediatrics at the New York Foundling Hospital. Postgraduate studies were pursued in Vienna before starting practice in New York in 1905. He soon received an appointment to the staff of Willard Parker and the Bellevue Hospitals and was made an attending pediatrist there. From 1920 to 1925 he was a clinical professor of pediatrics at the College of Physicians and Surgeons of Columbia University.

Roosevelt Hospital called him to the department of pediatrics in 1913 and under his leadership the service prospered. He gathered about him younger men whom he trained and for 25 years he fulfilled the exacting duties required, giving much of his time, in spite of an active practice and his many other obligations. In 1938 he was made a consultant to Roosevelt Hospital.

He was the recipient of almost every honor that pediatrics could bestow on a member of the specialty. He was a founder member of the American Academy of Pediatrics and became its president in 1937. He was also president of the American Pediatric Society and of the American Child Health Association. He was one of the nine members of the original board of directors of the Board of Pediatrics in 1932 and served on it for six years.

When in 1929 former President Herbert Hoover organized the first White House Conference on Child Health and Protection, he appointed Philip Van Ingen Chairman of the Committee on the Medical Care of Children. Van Ingen collaborated with the late Dr. Hamill and the late Dr. Blackfan in the preparation of the 1930 White House Conference Report.

With the declaration of war in 1917, he enlisted at once, with the rank of captain, and later, promoted to lieutenant colonel, he served in France and Italy in command of Field Hospital #331, receiving la Croce al Merito di Guerra for meritorious service.

Of his many accomplishments in the field of child welfare and pediatrics, none ranks higher than the service he performed for the New York Academy of Medicine, and especially in the compilation and publishing of *The New York Academy of Medicine: Its First Hundred Years*. Two years of his life were spent in the preparation of this volume, without financial return, and the New York Academy of Medicine shall be forever grateful for his splendid work in producing this great chronicle of its contributions to medicine.

Above all else, however, he will be remembered for his deep love for his children—the little patients who so often called him "Uncle Phil." To a friend who once asked him why he did not go away in the summer for a holiday, he replied characteristically, "I cannot leave my children." His services to children might well be epitomized by the motto, "non ministrari sed ministrare."

The last years of his life were devoted to the Roosevelt Hospital and the New York Academy of Medicine and to the many close friends he had made there. To the end, he was an integral part of these institutions he served so well. His many close friends in the American Pediatric Society and the American Academy of Pediatrics will miss him deeply in the years to come. During his turn as president of the American Academy of Pediatrics from 1937 to 1938, he rendered a fine stewardship and as one of the founder members he built well to insure the future growth of the Academy.

THE PHYSICIAN AND CHILD HEALTH SERVICES

An Interpretive Report and Guide to Local Planning

THE AMERICAN ACADEMY OF PEDIATRICS
610 Church Street, Evanston, Illinois

ACKNOWLEDGMENT

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INTRODUCTION

THE purpose of this report is to give physicians a better understanding of community health services for children. It attempts to outline how they developed, what areas of need are most acute, and what physicians can do, as private citizens as well as professional men, to take an effective and intelligent part in local and state planning for child health improvement.

The report is largely an outgrowth of the Academy's Study of Child Health, launched in 1946. Many physicians interested in child health services in their communities expressed a need for such a guide. The Study furnished valuable data not only on medical care and pediatric education, but also on the availability of public health services for children sponsored by both official and voluntary agencies. Data were gathered on hospital services, child health conferences, school health programs, services for physically handicapped children, mental hygiene clinics, public health nursing, and dental services. These data were presented, without interpretation, for the nation as a whole in the Academy's report, *Child Health Services and Pediatric Education,* which was published in 1949 by the Commonwealth Fund.

Since the material for the Study had been gathered by State Committees, many States published individual reports. A number of these included recommendations for improving child health services which have been carefully studied in the preparation of this guide. Additional material was obtained from the American Hospital Association, the American Public Health Association, individual members of the American Academy of Pediatrics, and from many other sources, as indicated in the bibliography on pages 27-28.

In reviewing some of these materials, especially the state reports, it was impossible not to be impressed with the amount of good will, active cooperation, financial aid, and other assistance which seems to be available to physicians in their own communities for constructive efforts in behalf of children. These assets can be used to full advantage, however, only if all physicians interested in child health will take a greater part in guiding the development of local and state child health services.

This report, of course, has many limitations. It presents the general what's and why's but cannot suggest many how's because of wide variations in local conditions. Nevertheless, it is hoped that it will be useful as a summary of the aims and functions of child health services, that it will stimulate interest, and suggest a few ways in which physicians can contribute toward developing needed health services for children in the communities they serve.

CHAPTER I

GROWTH AND DEVELOPMENT OF CHILD HEALTH SERVICES

THIS report covers only that segment of child health care provided through organized community agencies, official or voluntary. According to the American Academy of Pediatrics' Study,[1] about 22 percent of all the health care children received during an average day in 1946 for the nation as a whole was under such administrative arrangements. Most of the 22 percent represented hospital care, which is discussed in Chapter II. Only about 1.5 percent of total care on an average day represented care in child health clinics sponsored by public health agencies.

Origin of Public Services for Children

At the turn of the 20th century, bacteriology and immunology began to place in the hands of health officials the weapons to control communicable diseases and to prevent many deaths among children. These weapons made possible the development of planned, community-wide programs to prevent infant mortality and to improve child health.

The earliest efforts were made in cities, partly because high mortality and morbidity rates were obvious in urban areas and partly because health departments were first organized in major cities. Moreover, these localities usually had adequate numbers of philanthropic citizens interested in helping to create and support private as well as public health agencies. New York was one of the first cities in the United States to demonstrate how existing knowledge could be organized for widespread use to save the lives of babies in crowded sections. In 1893, Jacobi, one of the first American pediatricians, encouraged a New York philanthropist to establish milk stations for distributing pasteurized milk for New York infants to help prevent infantile diarrhea. By 1902, there were 14 such stations in New York. Between 1900 and 1910 a wave of similar infant welfare centers spread over the United States, and most major cities began to develop some child health services.

In 1908, the city of New York organized the first "Bureau of Child Hygiene" under Dr. Josephine Baker. Centers were established in poor and crowded sections where diphtheria immunization and smallpox vaccination could be given to large numbers of children in addition to medical guidance on infant care and feeding for mothers. Dr. Baker also saw the opportunity existing in public schools to have nurses follow up children with physical defects. Boston, however, was the first city in the United States to use physicians in public schools to examine children.

Private agencies took the initiative in caring for crippled children but most states soon recognized the necessity for making provisions for case-finding and treatment of handicapped children, at least those with serious orthopedic conditions.

With the exception of crippled children's programs, early services were primarily educational and preventive—usually school medical inspections under the control of educational authorities, and clinics for health supervision of babies. Then services were frequently initiated and supported by an interested group of citizens, including pediatricians

and other physicians. Usually these groups worked with or through a voluntary health agency, or a health department—sometimes both.

The medical profession, of course, recognized from the beginning the enormous benefit of the widespread application of preventive pediatrics. In 1909, a Conference on the Prevention of Infant Mortality was held under the auspices of the American Academy of Medicine, and this resulted in the organization of the American Association for the Study and Prevention of Infant Mortality at Yale University. Out of this grew the establishment of the American Child Hygiene Association which later merged with the Child Health Organization of America to become the American Child Health Association.

The government of the United States also recognized the value of child health care. One of the earliest federal agencies concerned with child health was the Children's Bureau, organized in 1912. The "Act for the Promotion of the Welfare of Maternity and Infancy" was another step in this direction. This was passed by Congress in 1921, and resulted in the rapid development of State Bureaus of Child Hygiene.

One section of the Social Security Act of 1935* stimulated the expansion of the maternal and child health services already organized by state health departments. Another is designed to strengthen crippled children's services which have developed under a variety of official and voluntary agencies in the states. Still another offers support for the establishment and maintenance of local public health services.

The extent of government interest in child health was demonstrated further at the Mid-Century White House Conference on Children and Youth[26] held in 1950—the fifth undertaking of this kind in 40 years. Efforts were made first to assemble what is known about child development and to find out where further knowledge is needed; second, to examine the environment in which children are growing up and to determine the extent of its influence; third, to study the ways in which home, school, church, and community are serving children's needs; fourth, to formulate proposals for improvement; and fifth, to suggest how these proposals can be communicated to the people, and acted on.

From the earliest days of pediatrics, individual physicians specializing in child care have been actively concerned with the welfare of all children. In many communities, they helped to develop general public health services as well as those directly concerned with child health. Because these efforts increased people's awareness of the value of medical services, they have also increased the demand for pediatric care and have benefited both pediatricians and general practitioners. This observation is supported by Study[1] findings which showed that public child health services are only a small fraction of the total health services for children; that public programs emphasize case-finding and referral to treatment resources in the community; and that 90 percent of medical care is in the hands of private practitioners. The study also showed that more child health care as well as the highest proportion of health supervision was given in the offices of the general practi-

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* "Title V, Part 1—Grants to States for Maternal and Child Welfare

Part 1—Maternal and Child Health Services

For the purpose of enabling each State to extend and improve . . . services for promoting the health of mothers and children, especially in rural areas and areas suffering from severe economic distress. . . .

"Title VI—Public Health Work

For the purpose of assisting States, counties, health districts, and other political subdivisions of the States in establishing and maintaining adequate public health services. . . ."

tioner and pediatrician who practiced in communities with well-developed health services. These findings should be an added incentive, if any be needed, for all physicians interested in child health to take the lead in supporting existing public health services and developing needed additional services in their own communities.

Areas of Need

The most significant finding of the Study was the disparity between urban and rural areas in availability of child health services, both public and private. This is particularly important in connection with public services for children because of the provisions of the Social Security Act of 1935. (See page 2.)

A factor of great importance in the creation of community health services is the existence in urban centers of organized health departments, voluntary agencies, and interested, informed, active lay and professional leadership. The challenge today is to help rural families achieve these same health benefits within the framework of the country's democratic institutions and financial resources.

In general, where child health services are deficient, other health facilities are also lacking. For example, as late as 1945, many rural areas did not have a basic public health organization. The American Public Health Association pointed out[30] at that time that one third of the population of the United States was not served by local health units which are essential to community health protection. By 1952, the National Health Council reports an increase in services, but states that some 28 percent of the population is still not covered by local health units.[31]

How can physicians help to strengthen and develop child health services? What leadership can the medical profession give in rural areas? This report cannot, of course, offer precise solutions to the problem. Too many local conditions determine the needs of a particular community and the possibilities of meeting them. It attempts, however, to offer suggestions on certain aspects of the problem and on some basic steps which can be taken not only by pediatricians but by all physicians in the community.

Suggestions for Local and State Planning

Each chapter will give suggestions for improving the specific child health service discussed. However, there are some activities which are basic and common to all child health services.

The history of the growth of child health services indicates that organized citizen activity is necessary to their development and improvement. Many of the state reports recommended a state health committee or council as one method of attacking the problem of improving child health on a state-wide basis.

State Health Councils

Members. In some states the members of the council have been appointed by the governor. In others it has been a committee consisting of members selected by each organization. In general, the following organizations should be represented: the state medical association; the pediatric society; the department of public health; the mental hygiene association; the dental association; nurses' associations; social welfare, and hospital associations; voluntary health groups; the Agriculture Extension Division, and any other lay or professional organizations interested in child health.

Sponsorship. It is usually helpful to enlist the sponsorship of influential and respected

citizens of the state such as the Governor, university presidents, outstanding religious leaders, philanthropists, and statesmen.

Purpose. The purpose of a state health council is to study health needs on a state-wide basis; to encourage the formation of local groups, where needed, to tackle local problems; and to help these local groups coordinate their efforts for greatest state-wide effectiveness.

Organization. It is important to use information already existing and work previously done whenever possible. Obviously, if an organization which will undertake to coordinate child health activities already exists at the state level, it should be used. This eliminates duplication of effort, enlists experienced personnel, and avoids antagonizing groups which may feel that their work is being usurped.

Probably the most logical way for such a group to start its study of health needs is to take a look at the map of the state. (Other organizations may have already divided the state into its natural subdivisions on a geographical basis or along routes of transportation. Many state agricultural divisions have already worked on methods of reaching their communities and rural areas.) When state subdivisions have been decided on, the health facilities of the state should be reviewed. This may consist of starting with the state survey done by the American Academy of Pediatrics, but should be supplemented by reports from the 1950 White House Conference[26] and from such organizations as the hospital association, mental hygiene association, the state health department, and any other state-wide health groups.

It is helpful to spot all these facilities on the map, in addition to the location of hospitals with beds or services for children. Hospitals, health centers, and laboratories still in the planning stage may also be indicated. The map should also show the communities with full-time or part-time health departments as well as county medical societies and other health organizations.

When the pattern of state facilities, available or planned, is clear, the group might turn to a study of the vital statistics to establish a clear pattern of needs. What is the state's infant mortality? What are the county figures? Do they differ in the various areas? Where, when, and how many cases of poliomyelitis have occurred? What is the statistical report on child accidents, tuberculosis, on rheumatic fever, on syphilis in children under 15 years of age? How many physically handicapped children has the state and how many mentally defective? What facilities, organizations and funds are available for the prevention and care of these and other conditions?

A state-wide group can be effective only to the degree that local units exist to study and follow through on the steps necessary to fill local health needs. One effective mechanism for this purpose is the local health council, which can draw together citizen leadership and representatives from influential groups in the community and focus their energies on solving local health problems. Physicians who have an opportunity to support or to take part in the development and activities of local and state health councils should do all they can to further its work. Much of the work described in various sections of this report can be done through such groups.

Local Health Councils

The health council movement has received support from the National Health Council, founded in 1921 by a group of national health organizations to coordinate and correlate the activities of the member organizations and to undertake other activities for the better-

ment of public health.[21] The American Academy of Pediatrics is now a member. Other groups which have given support to the health council movement are the state medical societies and the Committee on Rural Health of the American Medical Association.

Membership. In general, an effort should be made to bring together representatives from medical and allied professional groups—the local medical society, the local pediatric group, the dental society, the nurses' association, the local chapters of voluntary health agencies, safety groups, organizations for mental hygiene, the department of public health and welfare, school personnel, and any other local professional groups. Civic organizations and any citizens' groups which can be interested in health should also be represented. A program of help for children handicapped by rheumatic fever or some other condition has great appeal for many men's and women's clubs. The American Legion, for example, as well as other organizations, often have a health committee which either has or would like to have such a project to support.

Purpose. The purpose of a local health council is, first, to pool the information of the various organizations regarding needs, available facilities, funds, and personnel; and second to decide what steps can be taken to supply those needs.

Organization. Organization of the group may take place early or develop gradually as the study proceeds and takes form. There will be the usual officers, chairmen, secretary-treasurer, and standing or special committees as indicated.

It is advisable to have an operational plan and to select the necessary committees and sub-committees in order to cover the fields which need to be further studied or institute remedies for existing needs. The executive committee can then serve as a clearing house on health and medical care problems, programs, and facilities.

In large cities, organization on a city-wide basis may not succeed. A community soon reaches the size where it is not feasible to attempt to cover the city with one committee and it is better to divide it into sections or neighborhoods, each with its own health council and program. A city-wide council is indicated then as an intermediate step between these neighborhood study groups and the state council. In villages and towns in rural areas the council serves a particular need. In these areas many councils have already provided facilities for the care of the sick, and promoted educational programs in general. Funds from various groups have been tapped and much constructive work done.

When there are several local health councils in a state, each should have representation on the state committee and help to interest other communities in the formation of similar councils.

Public Health Departments

A well-functioning health department is essential in safeguarding the health of children. Every physician should work actively with his local and state health departments. These agencies are responsible, among other things, for the provision of safe milk, protection against botulism, trichinosis, malaria, taenia, hookworm, and various infectious diseases native to certain localities. Such programs for the control of environment are difficult for even a first-rate department of health to promote unless it receives full cooperation from all local physicians.

Where health departments are nonexistent or inadequate, physicians can stimulate interest among influential citizens in starting or improving this vital service. The type of health department that a community has is dependent largely upon its people. To provide one, it is usually necessary to raise funds by taxes, by a bond issue, or by some other

CHART I—ORGANIZATIONAL CHART

LOCAL HEALTH COUNCIL

Representation from Local Professional and Citizens Groups

Citizens Groups	Allied Professional Groups	County and District Medical Societies	Voluntary Health Associations	Governmental Agencies in Health
County & City Officers	Hospitals		Red Cross	Health Dept.
Business & Industry	Dental Society		Cancer Society	Public Welfare
Civic Organizations	Nurses' Association		Tb. Assn.	Economic Council
Church Groups	Pharmacies		Heart Assn.	Agr. Ext. Ser.
Labor Council	Veterinary Med. Assn.		Infantile Par.	Farmers Home Adm.
Schools—PTA	Prepayment Plans		Soc. for Crippled	Voc. Rehabilitation
Press, Radio, Theaters	Women's Auxiliaries		Mental Hygiene	
Farm Organizations			Safety Council, etc.	
Women's Clubs				

CHART II—OPERATIONAL CHART

LOCAL HEALTH COUNCIL

Representation from Local Professional and Citizens Groups

STANDING COMMITTEES	EXECUTIVE COMMITTEE	SPECIAL COMMITTEES
.....	Composed of chairman, vice-chairman, secretary-treasurer and committeemen	.....
Program		To be appointed as particular problems arise
.....		
.....		
.....		.....
Budget and Finance		
.....		
Publicity		
.....		
Publicity and Education		

means. Fund-raising measures may be defeated by the voters unless they are well informed about the need. Physicians can do a great deal to promote a good health department for their community by explaining to their patients and others what it will do for people and why one is needed. Physicians should also be familiar with the professional qualifications necessary for public health personnel and do all they possibly can to secure well-qualified personnel for their community.

CHAPTER II

HOSPITAL SERVICES FOR CHILDREN

THE practice of pediatrics, in its broadest aspects, parallels and is influenced by developments in the general field of medicine. At the same time, it possesses special characteristics largely dictated by the nature of the age group which it serves. Hospital care for children is influenced in the same way both by developments in the general field of hospital care and by the special needs of the pediatric age group.

Immediately preceding the collection of data for the pediatric study, the entire hospital field was surveyed by the Commission on Hospital Care. The results were published by the Commonwealth Fund in *Hospital Services in the United States*.[3] These data, plus those derived from the American Academy of Pediatric's study of child health services,[1] provide a rich background of information as to the amount and distribution of hospital facilities for children. In the latter study, attention was also given to quality of care.

Areas of Need

Amount and Distribution of Hospital Facilities for Children

Hospital services for children show the same trends which the Study[1] brought out in other fields—that facilities are more readily available in urban areas and poorest in the rural areas; that there are more in northeastern United States and less in the Southeast; that there are more and better facilities in the wealthy areas and fewer and poorer in the areas with a lower per capita income.

A number of communities have improved their hospital facilities independently, using the information in *Hospital Services in the United States*[3] as a guide in solving their problems. However, the Hospital Survey and Construction Act* (Hill-Burton Bill) which has stimulated and supported a nation-wide program for providing increased hospital facilities has been a major factor in hospital expansion. Through the Act, federal aid, financial and advisory, is made available through state agencies to areas of need which want improved hospital facilities. Throughout the country visible evidence of its effects can be seen in the form of new hospital buildings or improvements in many communities. The program represents an expenditure of many millions of dollars of both federal and local monies for systematic improvement of hospital services. Units for children, of course, have received a share of this over-all development because general hospitals allocate approximately 14 percent of their total beds to children.

Quality of Hospital Services for Children

This second broad consideration is far more complex and requires much more careful scrutiny than the relatively simple problem of providing adequate numbers of hospital beds and other facilities. The measurement of quality of pediatric care is difficult and it was possible to employ only the roughest indices in the pediatric study.[1] However, even with these admittedly imperfect and arbitrarily selected criteria, it is apparent that there is a wide divergence in quality and methods of hospital care for children. This finding of the study was, of course, not unanticipated.

* The purpose of this Act is to assist states in making an inventory of existing hospitals, to survey the need for new hospitals, and to develop a program for the construction of needed public and other nonprofit hospitals and health centers.

The difficulty in selecting criteria by which to measure quality of hospital care for children highlights the first need in any basic approach to this problem. Before any program for the improvement of quality can be developed, much clearer concepts of what constitutes good hospital services must be developed. Probably the most practical approach to the development of these concepts has already been begun in the form of attempts to set minimum standards for various aspects of hospital service for children. A milestone in these efforts is the *Manual on the Care of the Newborn and Premature Infant,*[5] published by the Committee on the Fetus and Newborn of the American Academy of Pediatrics. A companion set of minimum standards for formula preparation facilities prepared by a joint committee and published by the American Hospital Association is another such step. Another excellent source of standards can be found in the publications of the Federal Security Agency's Children's Bureau[4] which has been obliged to carry on extensive research in the field of child care in order to provide itself with effective tools for the administration of federal and state programs. Another less readily available source of material upon which to base minimum standards can be found in the various staff rules and regulations and methods of operation which have been developed by hospitals and hospital groups to meet specific needs.

Even with these fairly extensive sources of information, it is apparent that only the surface has been scratched so far as any attempt to reach universally acceptable and effective minimal standards for hospital care for children is concerned. There is need, therefore, for codification of existing standards as well as development of others. This will require some organizational control and leadership from pediatricians and other physicians concerned with child health care. Enlistment of counsel and participation from many other agencies such as hospital groups, governmental groups, dentists, and so on, is, of course, indicated. The American Academy of Pediatrics Committee on Hospitals and Dispensaries has begun to work on many of these problems.

Facilities for Education in Pediatrics

One of the most serious defects uncovered by the Study of Child Health Services[1] was the lack of adequate and easily available opportunities for postgraduate study in pediatrics by practicing physicians.

Probably the greatest single force for the improvement and progressive development of hospital services is their use as teaching ground for practicing physicians, residents, interns, nurses, physical therapists, nutritionists, and other ancillary personnel. Teaching is of primary importance because it provides a stimulus which almost automatically improves the quality of hospital services for children. This function is no longer vested only in the larger hospitals connected with medical schools but is now spreading to the smallest and most rural institutions. This is being brought about by regionalization of teaching as well as of service activities. Also, many state and local medical societies are developing their own postgraduate programs, employing visiting instructors who conduct local clinics and seminars instead of concentrating postgraduate teaching activities in the larger centers. Such programs, which use community hospitals for teaching, are the logical solution to this serious defect uncovered by the Study.

Changing Nature of Hospital Services for Children

A most important factor in the hospital picture is that of change. The practice of pediatrics, the concept of what makes up child health, is constantly changing to keep

pace with developments in medicine. These changes have been greatly accelerated during the past two decades. Most significant is the increasing emphasis on preventive pediatrics. Just as the physician now finds half of his practice among children devoted to preventive pediatrics, so must hospital care for children reflect this trend. Only a short while ago, hospital pediatrics were dominated largely by the infectious diseases. With the discovery of effective control measures, including antibiotic agents, these illnesses are making decreasing demands for beds. In their place there are patients hospitalized for correction of congenital defects which were formerly considered hopeless. Another group of patients now being more frequently recognized are those with the more subtle nutritional and metabolic disorders.

The old rigid isolation for the hospitalized child is giving way to adjustments dictated by these changes. Contagious disease hospitals and isolation units are dwindling in size to the point of disappearance. Where infection is present, modern techniques make it entirely feasible to care for the child in the pediatric department of a general hospital. This, of course, provides much greater flexibility in bed use to meet seasonal and other demands.

Starting with the resurgence of the rooming-in concept for newborns, some hospitals are recognizing the advantages of keeping intact the mother-child relationship when the child is hospitalized at any age. A natural corollary is the replacement of many hospital care days with a combination of home care and out-patient visits. These concepts are an outgrowth of the rapidly developing field of "mental health" which includes a whole battery of new diagnostic and treatment techniques to deal with behavior problems.

The place of the hospital in a community program for health supervision of well children requires careful exploration and planning. A modern hospital may include within its staff: pediatricians well-versed in child development and guidance; social workers familiar with community resources; pediatric nursing personnel; child psychiatrists and psychologists; dieticians well-grounded in the principles of normal nutrition; and dentists and dental technicians. Whether these individuals function independently and inefficiently or smoothly as a "team," frequently depends on the leadership of the physician in charge of child care.

Suggestions for Local and State Planning

Since improvement of hospital care for children depends upon the provision of an increased number of facilities of high quality, physicians should first familiarize themselves with the amount and quality of hospital services for children already in their communities.

One way in which physicians can help to increase hospital facilities for children is through support and guidance of any activity resulting from the Hospital Survey and Construction Act (see page 7) both at the local and state levels. Since federal funds must be matched locally, a great deal of community support and activity is needed to finance these projects.

New Hospitals

In communities planning new hospitals, physicians are in a position to provide informed leadership, and to see that an adequate number of beds for children are included. If necessary, appeal may be made to community groups to help provide funds or equipment for the pediatric department. For example, the women's auxiliary of one

church in a rural community supplies money for new linen used in the local hospital, and provides voluntary workers who keep used linens mended. Other groups provide scholarships for the training of nurses and technicians.

The laboratories, x-ray facilities, and pathological department are all important to diagnosis and therapy. If the hospital is not large enough to provide these diagnostic services, a liaison between a larger center could be sought. Arrangements may also be made for regular visiting consultants.

In states without a diagnostic laboratory, establishment of one will greatly aid the practicing physician by providing viral, bacteriological, and serological studies, and furnishing other aids. Such a laboratory may function through community hospitals or through a county health unit.

More Efficient Use of Existing Beds

Study of a local situation which has been tagged as a shortage of beds for children may show that much of the difficulty could be relieved by more efficient use of existing beds. Effective organization of the medical staff for pediatric care frequently will not only produce a more rapid turn-over of patients but also provide for more complete service to the individual child. Good organization can best be achieved if control of all child patients admitted to the hospital for any purpose is delegated to the pediatrician. He in turn, can then develop channels of consultation with other specialists so that a diagnostic and therapeutic program will be expeditiously carried on for each child. Such planning eliminates many hours or days of bed occupancy spent in waiting for consultations or diagnostic and therapeutic procedures. Modifications of such a plan will obviously be necessary due to many factors such as existing staff organization, personalities, space limitations, type of facilities available, and problems involving private patients.

Convalescent and Chronic Care

A second method of relieving demand for hospital beds is to develop within the community facilities for the care of convalescent and chronically ill children. Frequently the physician is not aware of all of the services available through city, state, or private agencies for such care. For example, he may not be informed about community resources in foster home care which, if properly handled, represents one of the most effective means of convalescent care. He may not make full use of the visiting nurse service available to patients in their own homes. If community resources for such care are found to be lacking or inadequate after investigation, physicians can provide the most effective leadership in stimulating the community to develop these important facilities. In attacking this problem the cooperation of an effective social service department within the hospital is invaluable.

There has been a decrease in the prevalence of orthopedic conditions needing hospitalization due to the reduction in incidence of tuberculosis and more effective control of bone infections. This development makes it desirable that institutions specializing in the care of certain handicaps review their functions in the light of changing conditions. Physicians connected with such institutions can be influential in expanding their services.

By developing and using resources such as these many pediatric beds can be made available which are now occupied by convalescent or chronic patients who do not require the expensive services of a general hospital but who are hospitalized simply because there

seems to be no other place where they can go. Sometimes medical progress has decreased the need for special hospital facilities set up in past years for specific conditions. The physician specializing in child care can provide the leadership and interpretation needed to divert such facilities to current medical problems. (See Chapter V, pages 19-22.)

Out-Patient Services

More extensive use of out-patient services is another effective means of relieving pressure on hospital beds. Traditionally, the out-patient department has been operated as a dispensary for low-income patients and not infrequently, from the staff standpoint, as a sort of medical stepchild to in-patient ward service. The changing character of medical and especially pediatric practice calls for more emphasis on the well child and the ambulatory patient. Early diagnosis, before the child's illness requires him to be a bed patient, is made increasingly possible by modern medical developments. A reorganization of the hospital out-patient department to include diagnostic and special clinics for referred full-pay patients can give direct relief for a crowded bed situation by providing care on an ambulatory basis which now frequently requires hospital admission. There are very few diagnostic procedures that cannot be performed on ambulatory patients by the hospital laboratories and x-ray departments.

It is apparent that most of the above discussion is applicable to adult patients and to most medical specialties as well as to pediatrics. The pediatrician can therefore expect to enlist ample support from his hospital staff colleagues in any program designed to improve patient care and to relieve pressures for hospital beds.

Premature Care

Prematurity is a costly problem and, as one of the leading causes of infant mortality, deserves community consideration. Cities with two or more hospitals will profit from the organization of a group of obstetricians, pediatricians, public health physicians, and nurses to analyze and discuss the causes of premature and infant deaths.

A study of local facilities and a survey to determine the number of trained personnel for premature care might be undertaken by the same group to promote greater interest in the premature program. The physicians from the public health department can make a special contribution to such a study by analysis of deaths which occur after infants leave the nursery and which therefore may escape the hospital statistical study. The public health physicians may also review conditions which appear during the first year, but which are not obvious in the nursery, such as retrolental fibroplasia, kernicterus, and other abnormalities.

Before a local plan is adopted, a study of methods used to reduce mortality of premature infants elsewhere should be made. The work in Birmingham, England, reported by Mary Crosse[17] presents one method. The Chicago plan of centralized care is another.

It is conceded that the highest mortality occurs during the first 24 or 48 hours and that transfer and handling of the infant increases mortality. Consideration should, therefore, be given to the training of personnel and the utilization of equipment at the place where the infant is born in order to avoid transfer and handling. Wherever possible, arrangements should be made to hospitalize mothers who go into labor prematurely at a center where there are special facilities for premature care. This is usually the best way to prevent both improper care at the place of delivery and transfer.

Regionalization

Another development in the hospital field which contributes greatly to patient care is the application of the principles of regionalization. Under such a system, hospitals establish affiliations with medical centers or large hospitals for the purpose of providing services which could not be supported by the individual hospital acting independently. Such a system may be limited simply to coverage of such ancillary services as x-ray and laboratory or may be developed into a highly integrated group administratively and medically. An outstanding example of the latter type of organization is the Rochester, N.Y., plan described in *Better Medical Care for Children.*[2] An important part of such a plan is the establishment of channels of medical consultation flowing out from the medical center to the smallest community hospitals. This is invaluable in planning a diagnostic and therapeutic program within the limits not only of the community hospital but of the entire organization.

Rural Health Centers

There is a growing trend to locate public health facilities within or adjacent to community hospitals. Even when these facilities are at some distance from the hospital, however, excellent integration is possible through common planning and the joint use of personnel concerned with the child whether he be sick or well. When this can be achieved, it will be found that all participants in the program are greatly strengthened in their capacity to provide improved child health services.

The American Medical Association and the rural health committees have studied the type of building suitable for rural health centers. These centers should be strategically located and provide facilities for clinics by visiting physicians who come at regular or irregular intervals, depending upon local needs and medical personnel available. In some areas it may be feasible to provide a bed for emergency patients awaiting transfer to a hospital. Transportation of patients from rural areas or rural health centers to hospital may be a necessary part of the program for the care of children in sparsely populated areas. This may be done by a voluntary agency. In one rural community, for example, the local volunteer fire department finances, houses, and provides volunteer drivers for an ambulance which serves the surrounding countryside.

The public health nurse is an indispensable health agent in rural communities. Funds for nurses' salaries, a trailer set-up for clinic work, or a health center for her headquarters may be indicated.

Pediatric Care Under Public Auspices

In many areas the care of the indigent sick is one of the responsibilities of the department of public health. Pediatric departments of county hospitals can be made excellent training centers for physicians interested in child care.

The adequacy of state institutions for children may also need the attention of physicians in the area. Are the number of beds adequate, the personnel properly trained, and the service in general as satisfactory as they might be?

States with Indian reservations within their boundaries have an additional group of children under public care who should interest the physicians of the area.

CHAPTER III

THE CHILD HEALTH CONFERENCE

THE earliest child health conferences were well-baby clinics whose main purpose was to save the lives of infants through the distribution of clean milk, and advice to mothers on proper feeding. Gradually, during the past 50 years, other factors became important. The purpose of a child health conference today is not only to save lives, but also to promote the best possible physical, mental, and emotional development. Services include periodic examination by a physician to see if a child is developing normally; immunizations; advice and guidance on feeding and behavior problems given by physicians and public health nurses; and referral to the physicians in the community for any needed treatment.

These developments parallel the evolution of child health supervision in the doctor's office. First, it consisted of advice on feeding. Then came emphasis on sanitation, hygiene, and prevention of disease. Now it also includes helping parents to understand the emotional and environmental factors which affect child growth and development and safety This changing emphasis demands a re-examination and re-evaluation of the techniques used.

Evaluation of Child Health Conferences

Health supervision in a child health conference has always had one drawback—the difficulty of coordinating sick and well care. No physician can do his best for a child, either sick or well, without full information concerning many factors in the child's life. Moreover, the line between sick and well is often so hard to draw that neither doctor nor parent is sure of it. And conflicting advice from two sources on what to do and when to do it adds to the parents' confusion.

The child health conference has, nevertheless, developed many assets. It has the possibility of obtaining specially trained physicians to carry on its activities. They can be expected to have a particular interest in this type of work and be willing to accept and profit by additional training in child growth and development. An effective child health conference also has the services of a public health nurse* who not only interprets the physician's advice in the clinic but goes into the home and helps the family carry out that advice. The service by the nurse is probably the key to the success of child health conferences which have survived even when they have had inadequate facilities and medical staff. Sometimes other special personnel are available, such as a nutritionist, a dentist, a psychiatrist, and psychologist. These services, except dental, are seldom direct to patients but more often take the form of consultation to the staff. The child health conference also provides a group experience for the mother which, if properly organized, is often extremely profitable in changing parental attitudes.

Areas of Need

Number and Distribution of Child Health Conferences

Although the child health conference is an established method of supplying health supervision for children who would otherwise not receive this care, the American Academy

* See Chapter VII, page 25.

of Pediatric Study[1] disclosed that such services are only a small part of the total health services for children. For the country as a whole, 62 children out of 1,000 under 5 years of age attended a child health conference in the year of the Study.[1] From state to state, this varied greatly from 265 per 1,000 children under 5 in the highest state to 6 in the lowest.

As might be expected health supervision for children was most lacking in rural and low economic areas where the services of private physicians were also lacking. These are the areas where leadership and support from physicians is most needed to develop community health services.

The fewer the number of physicians in these areas, the more essential child conferences are, to physicians themselves as well as to the children in the community. By concentrating health supervision of young children in a fixed place at a fixed time, a child health conference enables busy physicians to save time and strength as well as to accomplish more than they otherwise could in improving child health. Private practice also benefits. Study[1] findings showed that more child care and health supervision was given in the office of the private practitioner in areas which had well-developed child health conferences. This is not surprising because public health services not only emphasize case-finding and referral to community physicians for treatment, but also help parents to understand and appreciate the value of medical care.

Quality of Care

Among child health conferences that do exist, even an indirect look at the quality of care gave ample evidence that the general level is not high enough. Children are not followed over long enough periods; immunization procedures are often outmoded; and many physicians working in and supervising the conferences lack pediatric training.

How much more health supervision should young children have than is now being obtained? There is, of course, no precise answer to this question. But even in the states which rank highest in volume of health services,[1] infants and preschool children are receiving, through private practice and public agencies, only about two-thirds of the health supervision recommended by pediatric authorities. There is obvious need, in all parts of the country, for the development of more and better facilities for health supervision of well children and for education of the public and of physicians on the value of such preventive services.

Suggestions for Local and State Planning

The physician is in a position to improve the health supervision of children in many ways other than the work he does in his private practice. His avenues of contribution are the community, the hospitals, and the medical schools.

In the Community

In the community the physician can urge and work for the establishment of a local health unit, and adequate treatment facilities. (See Chapter I, pages 1-6.)

He can support and work actively with the American Academy of Pediatrics and other medical groups which are trying to encourage well-trained physicians to locate in areas which now lack physicians. When enough professional leadership is on the spot, it should be possible to develop child health supervision services as well as others.

He can help in the development of a voluntary or official visiting nurse service, a vital

part of child health conferences. (See Chapter VII, page 25.)

He can point up the need for child health supervision by calling the attention of community leaders to facts on infant and child mortality and morbidity; low immunization rates, as indicated upon admission to school; low economic and educational levels; minority groups or language difficulties; and inadequate medical or hospital services.

When a child health conference program is established, the leadership and work of physicians in the community will determine its success. Physicians with pediatric training have a special responsibility to work in the clinic, act on advisory committees, help to set standards, train other medical and nursing staff, and help in public education. Attention should be given to the most effective methods of using the time of physicians and nurses. Auxiliary workers and volunteers can be trained to do clerical and other nonprofessional jobs that wastefully occupy the time of the professional staff in too many cases. Improved methods of keeping records offer a fertile field for research. The American Public Health Association has recently prepared a report on the techniques and services of child health conferences entitled *Health Supervision of the Well Young Child With Especial Reference to the Child Health Conference* which should prove helpful to physicians sponsoring the development of such services.

In the Hospital (See Chapter II, pages 7-12.)

Out-patient clinics in existing or projected hospitals should include child health supervision in their programs or plans. Obviously, the importance of safeguarding the well child from exposure to sick children must be recognized and appropriate precautions taken. When child health conferences are held in outlying sections by travelling units, there should be close integration of these services with the treatment facilities, both public and private, that are available in the community.

In Medical Schools

The pediatrician who is affiliated with medical and other professional schools has an opportunity and a responsibility to emphasize child health conferences as well as other avenues of well-child care. He can utilize official and voluntary child health conferences for student training, and stress the importance of public health nursing and other aspects of community health work.

CHAPTER IV

SCHOOL HEALTH SERVICES

THE health of the child is primarily the family's responsibility. However, when the child reaches school age, some health protection service while he is in school has long been recognized as a community responsibility. The obvious importance of attention to the health of the school child and the relative ease of access to the child and the family during this period have been significant factors in the wide-spread establishment of school health services.

The first types of school health service were concerned with controlling the spread of communicable diseases among young children in crowded urban schools. When medical inspection for this purpose also revealed many neglected noncommunicable conditions, a number of cities employed nurses under the Board of Education or the health department to pass the information on to parents and to obtain treatment.

In the early years of this century serious communicable diseases such as smallpox, diphtheria, and trachoma were prevalent. The nuisance diseases such as scabies and pediculosis flourished. Many children did not see a physician from one year to the next. Under such conditions, almost any medical and nursing services were of benefit to children. Since then health conditions have changed rapidly. Today there is an increasing awareness that a different approach and emphasis are needed to discover current health problems and to make the best use of the valuable opportunities which the school affords for the health guidance of the child and his family.

Evaluation of the School Health Program

The American Academy of Pediatrics *Study of Child Health Services*[1] indicates that many of the opportunities to improve child health inherent in health supervision of the school-age child are used poorly, or not at all. The service, as now offered by many schools, is too often unrelated to the medical supervision which the child has had before entering school. It is often equally unrelated to the medical attention he receives during the periods when he is not under school jurisdiction such as vacations and after school hours.

Pediatricians play a relatively small part in direct service or as advisors in public school health programs for the country as a whole. The Study[1] showed that, of all physicians serving in the school, about 20 percent were health officers. Of the majority who were not health officers, 94 percent were general practitioners and only 4 percent were pediatricians. This means that school health programs lack the advice of the very physicians whose specialized understanding of child growth and development, and knowledge of the care and health needs of children, make them the best qualified to assist in planning a health program for school-age children. There is a possibility of real harm to a child examined by a physician not familiar enough with normal growth and development. Children have been falsely labeled as cardiac patients, endocrine cases, or described as having flat feet or bad tonsils when they were perhaps deviating only slightly from the average growth pattern. It is important that physicians and school administrators recognize the wisdom of having the advice of local pediatricians in developing school health

examination procedures and policies. Parents may be given false security by the school health examination. As commonly practiced, the examination is really nothing more than a screening test without the use of precision methods as aids to diagnosis. In their health education efforts, schools should make this very clear. Children as well as their parents should learn to use and rely upon the services of their own physician or clinic for final diagnosis as well as for treatment of illness.

A constant problem of many school health services is the difficulty of obtaining treatment for defects and health problems which have been found by the screening examinations in the school. Some of the reasons why parents do nothing about these health problems are: (1) the family does not really understand what needs to be done and why; (2) the school diagnosis cannot be verified by the family doctor or community clinic; (3) the child's school medical record is lost or contains insufficient information for effective follow-up by the school nurse or teacher; (4) the family is indifferent, or unable to pay for diagnosis and treatment; (5) the local practitioner may lack facilities for treating certain conditions, or there may be no facilities available locally. Clearer understanding of these and other factors present in individual cases might avoid some of the frustration and confusion which can interfere with the solution of the follow-up problem.

It is essential for the official education and health departments to recognize that solving this basic feature of school health service calls for coordinated planning and the cooperation of family physicians, dentists, specialists in child health, parents, and community health agencies.

Areas of Need

As in other health services, the first prerequisite is a sufficient number of physicians whose training and background qualify them for this particular position. School health service today calls less for a medical "inspector" who performs superficial medical examinations and more for a medical "advisor" on all aspects of the school health program. A school health program cannot be strong unless the participating physician has genuine interest in it, and appreciation of the opportunity which he has to improve child health, and some specialized understanding of child growth and development in addition to experience in the medical care of children.

As children grow old enough to become a part of the school system and community, former relationships with their family physician, health conferences, and clinics and hospitals need not—indeed should not—be severed. Much more coordination and cooperation between these groups and the official education and health departments are needed to avoid duplication of activities, procedures which are medically unsound, and misunderstandings. It is the child who suffers when the various agencies concerned with school health programs are not working closely together.

Suggestions for Local and State Planning

A better understanding of school and educational practices by community physicians is basic if school health services are to be improved. Practicing physicians can accomplish this by accepting every opportunity they have for collaborating with school personnel on plans for improving the health of children. Physicians who are connected with medical schools or teaching centers should promote the inclusion of experience in schools for undergraduate medical students and graduate students in pediatrics.

Another obvious opportunity for physicians to assist in the school health program is in helping to train the school staff to carry out the screening program. Teacher-observation and selection of children for medical examination is a more effective use of limited medical personnel in the schools than the use of physicians for routine annual or periodic examinations as now generally practiced. People who are not medically trained can do much, with careful instruction, to uncover health problems through observation and the more refined nondiagnostic tests which are available today. A screening method is, of course, an adjunct to careful examination. The school is not the place where a complete diagnostic procedure can be carried out. However, in conjunction with observation, the tests enable the examiner to have more factual evidence on which to base recommendations.

These tests should be worked out with the cooperation, understanding, and assistance of private physicians, clinics, hospitals, voluntary agencies, public health department and all other treatment resources in the community. When cooperation between these groups is well developed, there is little danger that any child who needs care will fail to get it for any reason.

Better coordination between education departments and child health groups has been accomplished in recent years by many communities through the organization of a local health council. (See pages 4-5.) By supporting and serving on such councils, physicians can make an invaluable contribution toward improving school health programs as well as other community health services for children.

CHAPTER V

SERVICES FOR PHYSICALLY HANDICAPPED CHILDREN

IN RECENT years, the definition of a physically handicapped child has broadened considerably. A child is now considered physically handicapped if he cannot, for physical reasons, participate in social, recreational, educational, or vocational activities on fairly equal terms with other children of his age. More effort must be put into research regarding the underlying causes of various handicapping conditions so that prevention may eventually replace programs of care. Meanwhile, it is realistic to plan for the early discovery and care of physical handicaps.

Areas of Need

Early Case Findings

The first effective step in efforts to keep permanent handicap to a minimum is to find cases as early as possible. If care is inadequate or delayed, a greater degree of handicap may be carried into adult life. This may lessen the individual's ability to take care of himself and make him a greater burden to the community.

Correct medical diagnosis is usually made with reasonable promptness in the more dramatic types of orthopedic handicaps seen in cases of poliomyelitis and osteomyelitis, for example. Delay in correct diagnosis is more general in other less obvious types of handicaps. For example, many registers of handicapped children kept by state agencies list very few children under school age with cerebral palsy, in relation to the number which might be expected from incidence figures.

The Study[1] indicated that the family physician usually has the first opportunity to detect potential handicaps, particularly among preschool-age children. If more medical schools gave their students training in diagnosing and treating conditions which produce handicaps, or even opportunities to observe handicapped children, family physicians would be able to make a greater contribution to prevention and to early case finding. In the absence of such training by many medical schools, pediatricians have the responsibility for making as much *pediatric consultation* as possible available to clinics and to all physicians and their handicapped patients who need it.

The school is a convenient place to focus case finding among school-age children. Heart disease and rheumatic fever are crippling conditions which warrant special mention. The activities of children with heart ailments should be of particular concern to someone in the schools. The onset of rheumatic fever usually occurs in the school-age period, and a school health examination may reveal the first evidence of it. The school is also a logical place to detect visual and auditory handicaps in their early stages.

A good periodic screening program (see page 18) carried out by well-trained teachers and school nurses, with suspected cases referred to the school physician for examination, is of great value in early case finding in this age group. It is essential to inform the child's parents of the suspected health problem and to help them understand the importance of early diagnosis in potential handicaps. Some families may also need assistance in obtaining adequate diagnostic services and treatment.

Prompt and Adequate Treatment

Early case finding is useful only if adequate treatment follows promptly. Because of the chronic nature of many physical handicaps, the cost of care is high. Diagnosis and treatment, therefore, are often community responsibilities. The Study[1] indicated that 90 percent of the visits which handicapped children made for care were to clinics operated by official agencies.

The Social Security program has helped to develop and improve services for physically handicapped children throughout the state, but much still remains to be done in many communities to meet the health needs of these children. Few states have programs which offer care for all handicapping conditions. Trained professional personnel including pediatricians, public health nurses, and social workers are often lacking. Psychometric appraisal, and other needed consultant services are seldom available. If all physically handicapped children are to have the variety and quality of services they need, both voluntary agencies and official clinical services for the handicapped should be strengthened.

*Hospital Care.** Resident care in hospitals is an important and expensive part of treatment. The number of hospitals specializing in the care of orthopedic conditions is large compared with the number of beds available to children for other conditions. Standards of care are quite high in these special hospitals and they are usually well staffed, with good medical, schooling, physiotherapy, and other necessary services. Social service is not uniformly available, but is increasing.

Special facilities for the care of convalescent or chronically ill children are a vast pediatric resource. The Study[1] showed that they supply one million days of care annually. In contrast to clinical services for handicapped children, only 6 percent of these institutions are operated by public agencies.

It is unfortunate that standards and quality of service in many of these institutions providing long-term care have not reached a desirable level. The Study[1] showed that only 58 percent were registered with the American Medical Association. Only one-third had laboratories for the most elementary tests; only one-fourth offered x-ray services; and only one-half had occupational therapists and social workers. With the recognition that convalescent care can no longer be accepted as primarily custodial, there is need to raise the quality of service given in convalescent homes and institutions for chronic care.

Convalescent care facilities are only one part of the total picture. It should be possible to choose the type of convalescent care best for each child, whether it be in his own home, in a foster home, or in an institution. Among the 95 institutions giving convalescent or long-term care in the group studied by the American Academy of Pediatrics,[1] only 11 percent used foster homes in their program of treatment.

Physicians need better training in the long-term care of convalescent handicapped children. Study[1] findings indicate that only 29 medical schools in the country give the pediatric department control over a number of beds for convalescent children. Often these beds are located in an institution too far from the department for its services to be effective. Few medical schools offer training in, or even opportunity for, observation of the care of convalescent handicapped children.

Continuity of Care. The physically handicapped child needs medical care over a period of years, usually throughout childhood. As soon as the condition is diagnosed, it is very often possible to map the stages during the child's growth when different services will

* See Chapter II, pages 7-12.

be needed, whether it be early surgery, special education, or eventual vocational training. Since a time-table of medical and related needs can usually be figured out in advance, a means to meet it should be established for each child so that he will be assured continuity of medical care. The interruption of medical supervision which occurs so often is costly. Communities need a mechanism for coordinating services for physically handicapped children to which private physicians and others giving these children care can report interruptions in medical supervision which come to their attention. In some communities, the health department offers this service. In other places it may be a hospital which is closely coordinated with the other health agencies.

Suggestions for Local and State Planning

Good care for physically handicapped children calls for especially close teamwork between members of the medical and other professions. One thing which every physician can do individually is to study the part which nurses, social workers, psychologists, physiotherapists, school personnel, and other professional workers play in the care of these children and to make every effort to work with all of them.

The Cardiac Program

With advances in heart surgery, the accurate diagnosis of congenital cardiac anomalies, and the selection of cases for surgery, has become almost a sub-specialty in pediatrics. Since the care of these cases is expensive, and the number of cases are relatively few in most areas, a state-wide program for the discovery and treatment of these cases of congenital heart disease should be incorporated into the rheumatic fever program.

Rheumatic Fever

A successful local program for the care of rheumatic fever cases requires, first, a careful, cooperative study of the situation in the community. Representative general practitioners, pediatricians, cardiologists, public health personnel, nurses, social workers, school personnel and lay groups should participate in such a study. A knowledge of the approximate number of cases in the community will indicate how important the problem is. Some type of registry may be indicated which should be designed to list the cases whose needs have not been met. If a registry is compiled, it is important that the file be kept confidential and that care be taken to see that checks and follow-up interviews are not used in any manner which may embarrass or annoy the patient or the private physician. As mentioned before, this program could include congenital heart disease.

The adequacy and costs of local facilities for diagnosis, for hospitalization of acutely ill patients, and for the care of chronically ill or convalescent patients should be studied. The source of funds and the amounts available should be checked against the patient load and cost of the care. The availability of trained personnel, including nurses and home study teachers, should be determined.

Proposals for the development of adequate local facilities for diagnosis, short- or long-term care, education of the public, training of personnel, and research studies can then be launched on a sound basis.

Poliomyelitis

State and local planning for poliomyelitis victims should be concerned with care of the acutely ill patient, provision for physiotherapy and rehabilitation of the subacute

case, and a long-term program for the permanently crippled individual.

The Acutely Ill Patient. The regulations drawn up jointly by the National Foundation for Infantile Paralysis, the American Public Health Association, and representation from the American Medical Association are available through the National Foundation for Infantile Paralysis and will serve a very useful purpose when the incidence of poliomyelitis increases in a community. They are of particular value in allaying parents' fears and answering questions concerning camps, playgrounds, theaters and schools.

If acutely ill patients can be admitted to a local hospital both for diagnostic studies and care during the febrile episode, many need no further therapy, because more than 50 percent escape without paralysis. These may then be followed by the private physician for any missed or residual weakness that might appear later. The acutely ill patient requiring respirator care or tracheotomy usually can be recognized in time for transferral. If there is a marked local increase in incidence of polio, a chest respirator for standby purposes might be borrowed. Respirators are tangible and dramatic and are often purchased by a community only to stand idle for years and be unfit for use when the emergency finally arises.

Opening county general hospitals to private physicians in attendance on patients suffering from polio would increase the number of patients cared for at the local level in small communities.

The Subacutely Ill Patient. In this category will be found many patients who need weeks or months of care in a hospital or in a convalescent home that has special accommodations. Hot packs, physiotherapy, and re-education in the proper use of involved muscles are needed over a period of time. Under expert therapy most of these patients regain good function. Centers strategically located throughout the state and in the larger cities should be prepared to offer such services to the surrounding area. These places also need an out-patient department where ambulatory patients can return for observation and follow-up therapy. (See pages 10-11.)

Severely crippled patients will need long-term planning. This may mean hospital care for one or even two years. It may also mean surgery, braces, and sometimes respiratory care for months or years. Children thus crippled should have facilities to continue their education. In most communities this can be done through the public school system. Some states offer a rehabilitation service with occupational therapy and prevocation opportunities.

Other Handicapping Conditions

Among other handicaps which may call for community attention are visual, hearing, and speech impairments; cerebral palsy; diabetes; and epilepsy. The official Crippled Children's Services of the Children's Bureau of the Federal Security Agency may be able to help with plans to increase over-all care for conditions which are not covered by specific state or local programs.

CHAPTER VI

MENTAL HYGIENE SERVICES

THERE is an increasing awareness in both professional and lay circles that community health services for infants and children should include consideration of mental hygiene principles along with those of physical care and treatment. There seem to be two main avenues open in the development of mental hygiene resources: (1) Through the development of child guidance or mental hygiene clinics which deal diagnostically and therapeutically with children and parents presenting problems due to emotional difficulties; (2) through educational opportunities within existing child care services. For example, prenatal clinics, child health conferences, day-care centers, nursery, elementary, and secondary schools, and others all offer opportunities to integrate consideration of emotional problems with the physical aspects of child care.

Areas of Need

Treatment Facilities

The Study[1] has shown that there is a definite lack of psychiatric services which offer parents and children help and treatment for emotional and behavior problems. Although the Public Health Service of the Federal Security Agency as well as private foundations have been helping the child guidance movement to spread considerably in the past years, the number of clinics is still far too small. A glance at the long "waiting list" of many of those now functioning indicates the great need.

Preventive Aspects

The need for treatment services is immediate and will unquestionably continue for a long time. However, the long-range solution to the problem of emotional ill health lies in finding out more about the causes of psychologic disturbances so that more effective preventive measures can be discovered and applied. Meanwhile, there is need for more attention to applying what are currently accepted as good mental hygiene principles in all contacts which physicians have with children and their parents in private practice as well as in community services.

Suggestions for Local and State Planning

As awareness of the value of child guidance clinics grows, more communities all over the country want to establish them, and are asking for help and advice. Physicians can encourage and support efforts made by state medical societies as well as the American Academy of Pediatrics and other national groups to further education of their members on the functions of these clinics. They can also join with others in their communities in working for the establishment of local diagnostic and therapeutic facilities in the field of mental health.

Physicians should support or promote the integration of child guidance into the training program of community hospitals. Group discussions of pediatric ward problems, the education of parents, and the training of nurses, occupational therapists, and others who come in contact with the child to be considerate and take a helpful attitude rather

than a disciplinary or authoritative attitude will greatly enhance the services of the hospital. Pediatricians have a special responsibility to assume leadership in such a program.

It is increasingly apparent that the core of good pediatric care is the ability of the physician to see the child as a living human being who has a genetic, cultural, physical, and psychological past; who lives constantly in relationship to other human beings, particularly parents, siblings and peers; and who is usually healthy much more of the time than he is sick.

Pediatric care should be focused on the broad aspects of growth and development. In practice, this means that physicians working in the prenatal clinic, child health conference, the school, and all other community agencies which have a share in child care must all do their part in providing for children's mental as well as physical health. To do this, many physicians need to have a better understanding of human beings. Some practitioners seem to be able to understand their patients' emotional needs without effort. Others, however, would feel more confident if they had guidance and instruction in these areas. Therefore, both physicians and nurses are requesting postgraduate courses and seminars in well-child work and in the psychologic aspects of pediatric practice.

A program designed to bring physicians and other professional personnel up-to-date on mental hygiene practices should include education on child accidents. Today the risk of death, serious disability, and permanent handicap from accidents is much greater than from disease. Physicians who supervise the health of children should be equipped to give more attention to this phase of child health, especially in the age group under 5. Factors which might be discussed to prepare physicians for offering accident prevention guidance include: (1) the chief accident hazards at various age levels beginning in infancy; (2) characteristic behavior and drives at various ages; (3) effect of parental attitudes and example; (4) physical and emotional environment; and (5) physical, emotional, and intellectual capacities of the child at various ages.

The program might also include suggestions on how individual physicians could include accident prevention education both in their private practice and in the community. A few ways in which this might be done are to keep literature on hand in private waiting rooms and clinics; to add some safety suggestions to diet lists; to study cases for clues to prevention; to investigate cases thoroughly and keep better records; to help in community education by talking to parent groups; and to form or join committees of local physicians who are working on the problem.

Physicians who are connected with medical schools or teaching centers can make an invaluable contribution to better mental hygiene services for children by fostering education in mental health. This should begin in undergraduate medical training days and continue through the postgraduate period. The kind of training which would give the undergraduate medical student a better understanding of comprehensive care would entail a drastic revision of much present-day curricula as well as a change in teaching methods. It would also call for great changes in the kind of pediatric training now being given in medical centers. Present teaching falls far short of preparing physicians adequately for certain responsibilities which they will meet later on in the care of children and prenatal patients.

CHAPTER VII

PUBLIC HEALTH NURSING

PUBLIC health nursing is not only the core of many community health services but also an essential part of the entire medical care structure of the community. Public health nurses make possible child health conferences, health supervision of school children, care for handicapped children, and communicable disease services as well as other programs of community health organizations. They also make home visits to provide bedside care to sick persons under a physician's care and to urge medical attention for those with health problems. It is impossible to measure the contribution of these shock troops in the health care of children. They are in the front line—in clinics, homes, and schools. They discover and refer many children who might otherwise get delayed or no medical attention. Their persistence in follow-ups helps to maintain continuity of medical care for children. By demonstration and other means, they also help to educate families about health and safety.

Areas of Need

The Study[1] showed a sharp difference between urban and rural areas in the availability of public health nurses. The contrast between these two areas in volume of nursing service was also great, just as it was for other types of medical service. This is understandable in terms of the history of organized community health services. Public health nurses work in health departments, visiting nurse associations, public schools, and industry. These institutions are developments primarily of urban areas. Although there is room for improvement in both quality and quantity of public health nursing services in cities, the real challenge lies in developing these services in areas where they are virtually nonexistent.

At the time the Study[1] was made, there were 1,065 counties in the United States which had no public health nursing service for children. Only 35 percent of nurses doing public health work elsewhere meet present academic standards in this field. There is also great need for more training for all nurses in the newer techniques, concepts, and problems of child health.

Suggestions for Local and State Planning

Physicians should encourage the use of public health nurses for community health services, especially in rural areas where the greatest need lies. In urban areas, physicians should make more use of the visiting nurse to provide better pediatric care for both sick and well children. Child health will benefit from closer teamwork between physicians and public health nurses.

Physicians should see to it that nursing organizations are always included in any community groups planning to improve child health care.

If there is no nursing organization in the community, physicians can be influential in establishing one. Detailed information and assistance can be obtained from the National Organization for Public Health Nursing on organizing local visiting nurse services.[19]

CHAPTER VIII

DENTAL SERVICES

WHEN the Study[1] was first projected, its content was a major theme of discussion. It is of interest that the Study Committee unanimously gave children's dental care a high priority among the items for examination. This decision was significant because pediatricians and general practitioners as a group are not particularly interested or well-informed in this area of medicine. It may have been their very lack of dental knowledge which promoted this part of the Study.

The question might be asked, "Is the over-all health of children correlated in any way with the condition of their teeth?" In one of the state reports, a correlation was made between the quality of medical services and dental facilities but this does not answer the question of the true relationship between dental health and over-all health. However, the Committee felt that dental health is generally accepted as an important item in a health program for children. Although the exact cause of tooth decay is not yet determined, it is known that restoration of cavities prolongs the life of the tooth.

Areas of Need

The findings of the Study[1] do not tell precisely how much dental care is actually required by children in various sections and communities in the country. However, even without exact information on the amount of dental care needed, it is evident that at present not even a minimal amount of dental service can be offered to every child in the United States.

The study of dental facilities for children shows that even states and counties which have the highest service ratings are unable to provide adequately for their entire child population. Even in New York and Massachusetts, for example, where facilities are well above the national average, children do not receive adequate dental care, appraised in terms of the dental profession's own criteria. In other words, the findings indicate that a high incidence of dental caries exists even in areas where dental facilities are most available, and that in isolated areas, especially in the South, little dental care is given.

Although accurate statistical data on the incidence of dental caries in this country is lacking, there is sufficient evidence to indicate that it is high. The great variation in facilities as shown by the Study[1] cannot in any way be regarded as an index of dental services needed in various regions. The discrepancies between what should be and what actually is available are indisputable.

If, in addition to the evident lack of general dental care of children, the fact is considered that pedodontists, orthodontists, and pedodontically trained general practitioners constitute only about 10 percent of the dental profession, the disproportion must be looked upon as much greater than noted in the Study.

From the findings, and from consultation with dental authorities, it is estimated that the dental profession in the United States is not equipped to give even minimal service, equitably distributed, to that 25 percent of the population which presumably needs it most. Redistribution of the available manpower cannot be expected to solve the problem or even greatly to ameliorate it. Undoubtedly more and better trained dentists are needed,

especially in children's dentistry, as well as more dental auxiliary personnel.

Above all, a more definite scientifically established concept is needed of the efficiency of present-day methods of symptomatic dental therapy. Granted that the filling and extraction of carious teeth contribute to child health improvement, these measures do not eradicate the basic etiologic factors responsible for dental disease. It seems questionable, therefore, whether the problem can be solved by expanding dental service along traditional lines. If dental service is to be considered a true health service, it might be made more efficient by better integration with other health services.

Suggestions for Local and State Planning

Physicians can assume responsibility for making sure that local dentists and dental societies are represented in all community groups working for child health.

Those associated with medical schools or teaching centers can promote the teaching of essential facts of stomatology. If dentists, in turn, promote the inclusion of the fundamentals of clinical medicine in dental schools, a start can be made toward better understanding of the place which dental services should have in child health services.

Physicians can help to integrate dental services with other public health services by supporting local and state health department efforts in this direction. Some state health departments, for example, are supplying dental service to isolated rural areas by employing their own dental personnel, and using mobile trailers and portable operating units.[28]

Another public health measure which physicians can support is the fluoridation of municipal water supplies. The Council of Dental Therapeutics of the American Dental Association is constantly re-examining reports on the safety and efficacy of fluoridation of public water supplies, and examining the claims made by persons who oppose fluoridation. The Council continues to reaffirm its recommendation of controlled fluoridation as a safe and effective dental health measure.[29]

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